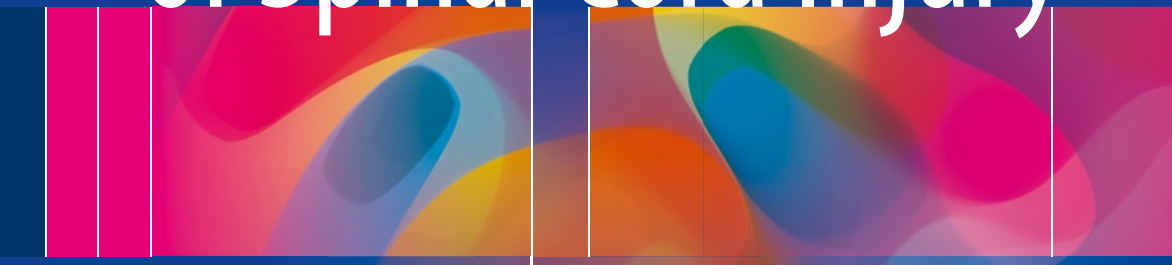
Neurological Aspects of Spinal Cord Injury



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Preface

Neurorehabilitation is a newer and smaller subspecialty in neurology and is largely dominated by neurologists concerned with stroke and brain injury. Spinal cord injury and disease has been more the realm of trauma physicians, spine surgeons, and physical medicine and rehabilitation doctors, but neurologists interested in this area are becoming more common for several reasons. For one, neurologists are specifically trained to detect, monitor, and treat neurological abnormalities. There is also a cultural tradition of research training, both clinical and preclinical, in neurological education with a growing interest in the areas of neural plasticity and neural repair. Finally, many are appreciating that lessons learned scientifically and clinically in spinal cord injury and disease may serve to enlighten investigations in other areas of neuropathology and provide new paths forward for those inquiries.

Until now, a comprehensive textbook specifically focused on addressing the neurological aspects (scientific and clinical) of spinal cord injury and disease has been missing. On the one hand, neurologists are less familiar with spinal cord injury and disease, since they are rarely exposed to this condition. On the other hand, spinal cord specialists coming from a variety of medical specialties other than neurology would like to obtain concise information regarding the neurological presentation, diagnosis, and treatment of spinal cord injury and disease.

Basics regarding epidemiology, anatomy, and pathophysiology as well as neurological signs and symptoms indicating lesions of the spinal cord including the cauda equina are provided. Differential diagnosis of nontraumatic spinal cord disease is extensively covered. Specific diagnostic procedures (imaging, neurophysiology), which allow one to differentiate various disease conditions, help to better predict the clinical outcome and, going forward, provide specific information regarding structural damage and/or neural repair. Spinal cord injury and disease causes not only the loss of normal neurological sensorimotor function but generates the emergence of pathoneurophysiology in the form of spasticity and neuropathic pain, both of which are extensively considered in this volume.

Spinal cord injury represents not just a disease condition with a segmental sensory and motor level in combination with below level loss of sensorimotor function. Damage to the autonomous nervous system leads to impairment of highly important body functions such as bladder/bowel evacuation, respiration and cardiovascular function, which are also covered here by leading experts.

Chronic neurological sequelae of spinal cord disease require a solid knowledge base as a prerequisite to properly treat symptoms, which can substantially affect quality of life beyond the immediate spinal cord injury or disease-related disability. It is rather difficult to identify an organ system not impacted by high spinal cord injury and disease and rather than consider this impact as pathology of those organ systems, one should consider the pathology being of lost neurological control. That is to say neurogenic bladder and detrusor/sphincter dysynergia are products of altered neuropathology and are not, at least initially, pathology of the bladder or urinary tract.

Beyond aspects related to acute care, neurorehabilitative concepts, with an emphasis on restorative approaches to recover function in both the upper and lower extremities, are discussed and will help those in the subspecialty of neurorehabilitation. Translational research approaches to protect and restore the nervous system after spinal cord injury are considered.

Many chapters go from bench to bedside with true translational (all the way to practice implications) intent. This will help clinicians to get an up-to-date overview regarding developing therapeutic strategies, which might further improve outcomes beyond the current state of acute and rehabilitative care.

The editors wish to congratulate all the contributing clinicians, therapists, and scientists, who have written such a comprehensive book. We are convinced that this book will provide new and valuable information to professionals dealing with the neurological aspects of spinal cord injury and disease in the clinical and research context.

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Part I

Basics

Epidemiology of Spinal Cord Injury

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Roland Thietje and Sven Hirschfeld

Abstract

Worldwide, the average prevalence of spinal cord injury (SCI) is estimated to be 1:1000, and the mean incidence is proposed to be between 4 and 9 cases per 100,000 population per year. Numbers vary substantially for different parts of the world. The mean incidence of SCI in developing countries is estimated to be 25.5/million/year with a range between 2.1 and 130.7/million/year. The incidence of SCI in industrialized countries ranges from 15 in Western Europe to 39/million/year in the USA. Most common causes for traumatic SCI are traffic accidents, falls, and results of violence, whereas the leading causes of non-traumatic SCI (NTSCI) are degenerative diseases and tumors (developed countries) and infections, particularly tuberculosis and HIV (developing countries). The majority of people with traumatic SCI are males (ratio men/women = 3:1), whereas in non-traumatic SCI, genders are almost equally distributed. Worldwide NTSCI increases significantly as well as the number of high-level tetraplegic patients with the need for permanent or artificial ventilation. In general, the percentage of tetraplegic patients has increased and nowadays equals that of paraplegic patients. Additionally, in industrialized countries, the mean age at the time of injury increases continuously, mostly due to older patients also experiencing SCI. The mortality rate in the first phase after SCI is directly linked to the availability and quality of primary care and rehabilitation approaches. Life expectancy is determined by the level of integration into a proper socioeconomic environment after initial treatment and directly related to the availability of qualified medical care in the event of complications such as pressure ulcers or urological problems.

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1.1 Introduction

In order to understand the sociopolitical, health-related, and socioeconomic implication of spinal cord injury (SCI), knowledge about the frequency of occurrence and etiology is required.

This introductory chapter provides basic numbers on prevalence, incidence, mortality, causes of death, and treatment costs of SCI. In particular, the differences between traumatic and non-traumatic causes of SCI and also between regions with high and low income will be elaborated. A correct interpretation of regional differences is of utmost importance, because it allows for a prognosis of the course of numbers in developing and emerging countries.

The presented results are based on the review of the scientific literature and of reports of public administrations of different countries up to 2015 with a strong focus on the most recent available numbers and information.

1.2 Challenges in Interpretation of Epidemiological Data

Unfortunately, a central worldwide registry for the collection of epidemiological data regarding SCI does not exist. Additionally, even industrialized countries do not often have a national SCI registry, in which data, at least from SCI centers about new cases, are collected. Population-based surveys for estimation of the percentage of persons with SCI in the general population are very rare [1]. Most of the epidemiological data on incidence and prevalence represent extrapolations based on the numbers collected by a few clinical centers or based on assumptions about the mean life expectancy of individuals after SCI, respectively. Due to the different methodologies of data collection and various assumptions, epidemiological data available from the literature usually have a high variance, which makes it impossible to compare data from different sources. There is very sparse information if patients with lesions at the level of the cauda equina or conus medullaris, which results in lesion of peripheral nerves, are classified as patients with SCI and are included in the epidemiological data analysis or not. Even though the incidence and prevalence of cauda equina lesions is relatively low [2], it might explain some of the variations of the data between different sources. The same applies to congenital SCI (spina bifida, meningomyelocele), for which the incidence is estimated to range between 2 and 58 per 10,000 population per year [1].

Epidemiological data might change very rapidly and numbers, which were valid a decade ago, might be obsolete nowadays. This becomes most apparent in countries with high average income, where life expectancy has dramatically increased over the last two to three decades [3].

Especially the rapid increase of cases with non-traumatic SCI within the last few years shows that the date of data acquisition is of significant importance and, as a further consequence, renders the comparison of data from different sources rather impossible.

Especially, data on prevalence and incidence of individuals with tetraplegia due to high SCI with the need for permanent mechanical ventilation or a phrenic nerve stimulator is poor. One of the reasons is that those patients die early after SCI in many countries, even in those with high average income, because either the required medical-technical care cannot be provided or the social system does not contribute financially to home-based ventilation.

1.3 Prevalence of SCI

In general, the term prevalence describes the proportion of a population living with a certain condition. It is determined by comparing the number of people found to have the condition with the total number of people studied and is usually expressed as a fraction, as a percentage, or as the number of cases per million people. Point prevalence is the proportion of a population that has the condition at a specific point in time. Period prevalence is the proportion of a population that has the condition at some time during a given period (e.g., 12-month prevalence) and includes people who already have the condition at the start of the study period as well as those who acquire it during that period. Lifetime prevalence is the proportion of a population that at some point in their life have experienced the condition. Lifetime prevalence is the term that is often only called "prevalence" in medicine [4]. It is determined by the number of new cases per year and the life expectancy of people with this condition in years. As a consequence prevalence is, on the one side, an estimate for the hazard potential within a society and, on the other side, an indicator for the effectiveness of secondary preventive measures.

A report of the World Health Organization (WHO) shows that 15 % of the world's population is affected by disability, 0.1 % by spinal cord injury [1]. Hence, the global prevalence of traumatic SCI is estimated to be 1000/million people [5]. However, this number needs to be treated with caution, because it represents only a rough estimate as valid data are available only for a few countries (Table 1.1). Even less reliable data are available on the prevalence of non-traumatic SCI (Table 1.2).

In general, the incidence of traumatic SCI varies substantially between countries. Among the reasons for these country-level variations are genuine country-level differences in incidence related to differences in risk, standard of living and health-care systems, merging of data from adolescents and children (studies reporting only adult incidence overestimate the overall population rate), and differences attributable to methodological approaches. A big problem arises regarding the representativeness of the data, because only a few, mostly (small) countries, have a country-wide SCI registry system, such as Finland or Scotland, and therefore incidence estimates are extrapolated from city or regional data that may not be representative for the country as a whole [1]. It is remarkable that the overall prevalence of SCI (traumatic and non-traumatic) in Iran is with 318/million population, one of the lowest worldwide [14].

Table 1.1 Prevalence of traumatic SCI

Country	Year	Prevalence (cases/million population)
USA [6]	2013	906
Canada [7]	2010	1298
Norway [8]	2002	365
Finland [9]	1999	280
Australia [10]	1997	681
Germany [11]	2015	500
France [1]	2014	250

Table 1.2 Prevalence of non-traumatic SCI

Country	Year	Prevalence (cases/million population)
Canada [7]	2010	1120
Australia [12]	2013	455
Germany [11]	2015	300
India [13]	1986	2310

1.4 Incidence of SCI

While prevalence is a measurement of all individuals affected by a condition at a particular time, incidence is a measurement of the number of new individuals who acquire a condition during a particular period of time. The incidence of SCI describes how many people have acquired an injury of the spinal cord within a predefined period of time. It is therefore a descriptive term for the risk of suffering from a certain condition or disease and represents an indirect indicator for the effectiveness of primary preventive measures.

The incidence of SCI including traumatic and non-traumatic lesions is estimated to be between 40 and 83/million/year, with an absolute estimated annual number of new cases worldwide around 250,000–500,000 [15]. The worldwide incidence of only traumatic SCI is estimated to be between 10.4 and 83/million/year [13].

However, these numbers must be interpreted with caution. The determination of the incidence of SCI is highly dependent on a variety of factors, which results in large variations.

Patients with traumatic SCI who die at the scene of the accident or pass away on their way to an emergency room are normally not included in any statistical data evaluation. This also applies to patients with a malignant disease in its final stage involving an SCI. These facts introduce a systematic bias to the overall incidence of SCI resulting in lower estimate.

Similar to the problem of determining a representative value for the prevalence of SCI, the database for determining the incidence of SCI is incomplete and

inconsistent. Technical limitations and a systematic bias may be present in data collection in different countries. As a consequence, there are only rough estimates available.

Published data from different countries show enormous differences in the average incidence of SCI [7, 16, 17]. These differences might be explained by different age distributions, hazard potentials, and different levels of emergency treatment. According to a study, the annual incidence of new traumatic SCI rose significantly in persons 55 years and older. The proportion of tetraplegia and of incomplete injuries also increased. Additionally traumatic SCI occurs mostly at a young age, below 30 years [18, 19], whereas non-traumatic spinal cord disease affects people at a higher age, above 55 years.

In war zones or countries with a widespread availability of weapons or a high crime rate, the number of traumatic SCI is high, whereas gunshots or other forms of violence as causes for SCI play only a minor role in countries with restrictive laws on fire arms [20, 21]. The incidence of traumatic SCI in the mentioned countries and regions (Table 1.3) varies between 12 and 53/million [7, 10, 17, 24]. Even if data on the overall incidence are available for a large country, the regional incidence may vary to a large extent due to differences in industrialization and medical infrastructure, e.g., rural areas versus cities.

The incidence of non-traumatic SCI varies between 12 and 76/million population [7, 10, 26–28] (Table 1.4). In western industrial countries, the demographic change toward a dramatic increase in the elderly population has an enormous

Table 1.3 Incidence of traumatic SCI in individual countries and WHO regions

Country	*Year*	*Incidence* (*cases/million population/year*)
Germany [11]	2015	13
Canada [7]	2010	53
Scotland [20]	2015	15.9
Australia [22]	2015	21–32
Finland [23]	2014	25
Netherlands [24]	1994	12
WHO region	*Year*	*Incidence* (*cases/million population/year*)
Western Europe median [25]	2011	16
North America, high-income median [25]	2011	40
Asia Central [6]	2011	25
Asia South [6]	2011	21
Caribbean [6]	2011	19
Latin America Andean [6]	2011	19
Latin America Central [6]	2011	24
Latin America Southern [6]	2011	25
Sub-Saharan Africa Central [6]	2011	29
Sub-Saharan Africa East [6]	2011	21

Table 1.4 Incidence of non-traumatic SCI in individual countries and WHO regions

Country	*Year*	*Incidence* (*cases/million population/year*)
Germany [11]	2015	12
Canada [7]	2010	68
Scotland [20]	2015	2.8
Australia [10]	2005	26
Spain [29]	1999	11
WHO region	*Year*	*Incidence* (*cases/million population/year*)
Western Europe median [27]	2011	6
North America, high-income median [27]	2011	76
Australasia [27]	2011	26
Asia Pacific [27]	2011	20
Oceania [27]	2011	9

Table 1.5 Distribution of gender in traumatic SCI

Continent	Year	Male [%]	Female [%]
Europe (Germany) [11]	2015	76.8	23.7
Africa [31]	2013	81.1	18.9
Canada [7]	2012	71.6	28.4
Asia [32]	2015	70.2	29.8
North America [33]	2004	74.6	25.4
Latin America [21]	2015	78.2	21.8
Australia [34]	2011	71.6	28.4

Table 1.6 Distribution of gender in non-traumatic SCI

Continent	Year	Male [%]	Female [%]
Europe (Germany) [11]	2014	60.4	39.6
Africa [36]	1994	67.9	32.1
Canada [35]	2010	57.2	42.8
Asia [37]	2013	67.3	32.7
North America [38]	1999	66.3	33.7
South America [39]	2011	50.5	49.5
Australia [12]	2013	53.9	46.1

influence on the etiology of SCI, meaning that the percentage of non-traumatic SCI is constantly growing over the last decade [30].

With regard to gender, men are by far more affected by traumatic SCI [7, 24, 31] (Table 1.5). In case of non-traumatic SCI, the proportion of females is nearly equal to males [12, 29, 35] (Table 1.6). Respective gender proportions are robust and comparable in all countries worldwide.

1.5 Etiology of Traumatic SCI

The most common global causes for traumatic SCI are road traffic accidents followed by falls and violence. The proportion of road traffic accident-related SCI varies to a great degree for different regions of the world. The number of road traffic accidents is directly related to the population and traffic density but also depends on regionally quite differently developed road safety measures. In Africa, for instance, the proportion of traffic accident-related SCI (57 %) is almost twice as high as in Europe [31, 40], whereas the probability of a fall-related SCI in Europe is nearly twice as high as compared to Africa [31, 35]. A Chinese study shows that rapid progress in industrialization and the associated increase of traffic substantially influence the incidence and causes of traumatic SCI. Between 2000 and 2010, an increase of road traffic accident-related SCI to 51.2 % has been reported [41]. In other developing countries, traffic accidents are by far the most prominent cause of traumatic SCI (77 % in Lagos [42]). With 85 % the highest proportion of traffic accident-related SCI can be found in Saudi Arabia [43].

In children and juveniles, traffic accidents are the most common cause of paralysis worldwide. In the group of children with an age below 12 years, traffic accidents are the most frequent cause of traumatic SCI, higher than all other causes together [18, 19]. In the subpopulation with an age below 45 years, traffic accidents are the most common cause of SCI. However, after the age of 45, falls are the most likely cause for an SCI [20].

However, those numbers need to be seen from the perspective of regionally different populations. As an example, the high percentage of fall-related SCIs in older people in Europe can be easily explained by the demographic population structure in European countries [1]. This development is also found in the USA ("mean age at injury increased 9 years since the 1970s") [43], in Canada ("significant increase in the mean age at injury from 30.23 to 45.768 years of age") [44], and in Australia reporting a significantly increasing rate of fall-related injuries in elderly males [45].

People's recreational and sport-related activities influence both the rate of SCI and the associated patterns of injury. The percentage of sport-related SCI in the overall traumatic SCI population is 1.7 % in Nigeria, 4.0 % in Germany, 10.0 % in the USA, and 14.1 % in the Netherlands [11, 28, 42, 46]. According to the available literature, there are six countries in which sports accounts for over 13 % of SCI (highest to lowest: Russia, Fiji, New Zealand, Iceland, France, and Canada). Diving, skiing, rugby, and horseback riding were identified as individual sports with the highest risk for SCI. For hockey, skiing, diving, and American football, almost all injuries are located at the cervical spinal cord level, while over half of horseback riding and snowboarding injuries are at the thoracic or lumbosacral level [47].

The number of traumatic SCI caused by firearms varies to a large extent in different countries. In Northern Europe the percentage is below 1 % of the overall traumatic SCI population, whereas in Brazil injuries of the spinal cord by the use of firearms are a common cause accounting for 16.9 % of all traumatic SCI cases [48].

As mentioned above the incidence represents, among other things, a good indicator in terms of effectiveness of primary measures for the prevention of SCI. For the validity of this statement, there are both positive and negative examples: in Germany the costs of treatment after accidents during work will be covered by a separate statutory accident insurance (workmen's compensation). This is somehow a unique approach in the international context. The data from Germany show that the proportion of SCI caused by workplace accidents has decreased from 22 to 7 % of the total traumatic SCI population from 1985 to 2013 [11]. This can be attributed both to the lower risks for workplace-related injuries due to the general trend toward a modern industrial and information society with more indoor work places and also to the implementation of stricter occupational safety regulations. The latter is without doubt an example of successful primary prevention.

However, in another cause of traumatic SCI, diving into shallow water, primary preventive measures seem to be less effective. Data from Germany show that the percentage of cervical lesions resulting from shallow water diving persists on a constant level from 1985 to 2013 [11]. The proportion of SCI related to shallow water diving accounts for approximately 4 % of traumatic SCI. The introduction of several prevention campaigns did not yield a lower incidence. In contrast, prevention programs in the USA and Canada have been reported to successfully promote reduced rates of diving into shallow water accidents [49].

1.6 Etiology of Non-traumatic SCI

Few studies provide epidemiological data on non-traumatic SCI. Non-traumatic SCI has received more and more attention over the recent decades, whereas until the mid of the twentieth century, the percentage of traumatic SCI was reported to be more than 90 % with only few cases due to non-traumatic causes. The increase of non-traumatic SCI – a disease of the elderly – can, for the most part, be explained by the increase in life expectancy of the population in developed countries. This trend is normally linked to the occurrence of age-related diseases such as cardiovascular disorders, tumors, and infections of the spinal column or spinal cord itself. Developing countries tended to have a higher proportion of infections, particularly tuberculosis and HIV, although a number also reported tumors as a major cause [27].

A detailed analysis of over 1000 cases of non-traumatic SCI in 2012 in Germany attributed 26 % to tumors compressing the spinal cord, 20 % to infectious disease, and 16 % to ischemia. The most common non-traumatic cause (41 %) was degenerative spine diseases with associated spinal canal stenosis [11]. These proportions are comparable for all industrialized countries [26].

Non-traumatic SCI results much more often in incomplete paralysis compared to traumatic SCI [9, 11, 12, 26, 28, 29, 41, 42] (Tables 1.7 and 1.8).

Table 1.7 Distribution of lesion level and severity in traumatic SCI

Continent	Year	Tetraplegia		Paraplegia	
		Complete (AIS A) [%]	Incomplete [%]	Complete (AIS A) [%]	Incomplete [%]
Europe (Germany) [11]	2015	28.6	25.0	30.1	16.3
Middle East [50]	2012	21.0	31.0	29.0	18.0
Asia [41]	2013	26.8	25.7	23.7	8.3

Table 1.8 Distribution of lesion level and severity in non-traumatic SCI

Continent	Year	Tetraplegia		Paraplegia	
		Complete (AIS A) [%]	Incomplete [%]	Complete (AIS A) [%]	Incomplete [%]
Europe (Germany) [11]	2015	7.3	20.6	29.7	42.2
Middle East [50]	2010	11.9	25.1	15.9	47.1
Australia [12]	2013	19.4	11.3	20.2	49.1

1.7 Trends, Mortality, and Life Expectancy in SCI

Until the beginning of the twentieth century, an SCI was a devastating condition leading to death due to pneumonia, pressure sores, or lower and upper urinary tract infections within days to months depending on the lesion level and severity. In particular, in high cervical cord lesions very soon after the injury, pneumonia occurred due to the impairment of respiratory function, which in the long run, led to death due to the lack of therapeutic interventions. The progress in the second half of the twentieth century in the development of surgical stabilization options and intensive care medicine as well as a strong desire to not accept the unavoidable fate of SCI victims, resulted in the introduction of dedicated rehabilitative and neurological therapies. These factors promoted a fundamental change in the situation of individuals suffering from the sequels of SCI.

As a consequence, the life expectancy of people with traumatic SCI has continuously increased over the last 70 years [51]. However, compared to the general population, mortality is increased in the SCI population. The life expectancy (LE) of people with SCI is still lower compared to age-matched able-bodied individuals. The highest estimated lost LE was associated with chronic pressure ulcers (50.3 %), followed by amputations (35.4 %), one or more recent hospitalizations (18.5 %), and the diagnosis of probable major depression (18 %). Symptoms of infections were associated with a 6.7 % reduction in LE for an increase in infectious symptoms [52]. For patients with traumatic SCI, the highest mortality risk is during the first year after the date of injury and the onset of SCI [53, 54].

The mortality rate and life expectancy after SCI differ substantially in different parts of the world mainly due to enormous differences in the standard of care. This includes, on the one hand, the availability and effectiveness of emergency units and, on the other hand, the quality of lifelong care [55]. The quality of emergency and primary care and the subsequent medical-rehabilitative therapy affect mortality rates to a great extent. Particularly in low-income countries, many people today still die from complications that could easily be avoided with a higher standard of care.

In addition to the level and severity of the SCI, the presence and extent of concomitant injuries and trauma strongly influence the mortality risk. Age substantially influences the prognosis of survival due to the presence of comorbidities [56].

The mean life expectancy of people with tetraplegia is lower than of persons with paraplegia. A complete SCI results more often in earlier death than an incomplete SCI. This was shown in a number of countries by comparing mortality rates with the general population [53, 57].

Several studies show that in people with paraplegia, the causes of death become similar to those of the general population [53, 58]. Most common causes of death are nowadays ischemic events such as cardiac arrest or stroke, tumors, and chronic obstructive pulmonary disease (COPD). However, approximately 15 % of SCI patients still die because of pressure sores and their medical consequences [58, 59].

The causes of death in people with tetraplegia are very different to those with paraplegia. In the international literature, high numbers of pulmonary complications are found consistently to be a leading cause of death in people with tetraplegia [30, 60–62]. This is obvious and, particularly in case of very high lesions with an extended paralysis, unavoidable to some extent. In any case, patients suffering from very high cervical SCI require permanent mechanical ventilation and form a special group. Unlike any other group, their mortality depends on the availability of medical-technical equipment and nursing care. Therefore, the mortality rate of these very high-lesioned patients may serve as an indicator of how much a society is technically and economically able to provide a high-level of community-based care [63].

Independent from the severity and the level of the lesion, there is evidence that the incidence of suicide as a cause of death is higher in the SCI population than in the general population [64]. This might be related to the fact that a suicide attempt was quite often the cause of the SCI [65].

Other typical paralysis-related causes of death are chronic obstipation related to neurogenic bowel dysfunction and urosepsis as consequences of neurogenic bladder dysfunction. Not infrequently, urothelial carcinoma of the bladder can represent a death-related cause in SCI patients [50].

The notable shift in traumatic SCI toward older patients has a huge impact on rehabilitation approaches, because older people have age-associated comorbidities limiting their rehabilitation potential [46, 66, 67]. This problem will become even further apparent due to the ongoing demographic change in industrial countries. A German population of over 3.000 SCI patients collected over a 25-year period showed that 84 % of the patients suffered from comorbidities such as cardiovascular diseases and tumors, which required additional treatment [11].

Trends in the growth of the proportion of non-traumatic SCI can be seen in the German database, to which all German SCI centers contribute. In the beginning of data acquisition (1976), the proportion of non-traumatic SCI was 14 %. In 2012, the percentage of non-traumatic SCI was 54 % [11], with an average of 37 % between 1976 and 2012.

1.8 Costs of SCI

SCI does not only put additional burden on to affected individuals, but it generates substantial costs for health care and professional reintegration. In many instances, the severity of the functional impairments with required lifelong care substantially contributes to this figure. The costs on the social system are very high due to permanent paralysis. Here, one has to differentiate between costs directly related to the injury and the expenses of the treatment of the lifelong consequences of the SCI impairment, which also include financial commitments of social reintegration.

Basically, direct costs in the acute phase after the injury consist of:

- Expenses resulting from rescue and emergency services in the case of traumatic SCI
- Costs for inpatient surgical and conservative treatments and care
- Costs for outpatient care, medication, physical/occupational therapy, assistive devices such as wheelchairs, and consumables such as catheters

Costs related to comprehensive care are mainly generated by:

- Setup of an accessible home and eventually also a working environment
- Loss of tax and/or welfare expenses in case professional reintegration is not successful

It is clear that both the severity of the functional impairment and the outcome of the primary medical treatment and the medical and professional rehabilitation have an impact on both direct and indirect costs. The highest costs occur during the first year after injury, whereas the total costs are determined by the life expectancy.

Published data regarding lifetime costs of SCI are inconsistent and often untransparent regarding the method of estimation [1]. The available numbers often seem to be outdated and in any case need to be interpreted with caution. Therefore, no precise numbers are provided within this chapter.

Conclusions

Epidemiological data on incidence, prevalence, and etiology of traumatic and non-traumatic SCI are subject to substantial regional variations. These numbers are influenced by multiple factors, most importantly the level and availability of emergency and life-saving services as well as SCI-specific surgical, rehabilitative, and home care institutions. Trends in the incidence of traumatic SCI over

time may serve as an indicator for the success of preventive measures. The increase in life expectancy of the general population in societies with high average income results in an increase of non-traumatic SCI. More population-based studies are needed to obtain more reliable data about SCI epidemiology and trends over time.

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Functional Neuroanatomy of the Spinal Cord

2

Maren Engelhardt and Jürgen-Markus Sobotzik

Abstract

The spinal cord (SC) is the part of the central nervous system (CNS) that is responsible for the motor, somato-sensory, and visceral innervation of the extremities, trunk, and large parts of the neck as well as all inner organs. Spinal nerves of the peripheral nervous system (PNS) serve as connections between the CNS and distal receptors and organs. And just as the SC controls many aspects of locomotion and visceral function, it also serves as an important relay station for incoming, afferent information from the periphery to central brain regions. It thus constitutes the major coordination hub for how humans unconsciously perceive their periphery and how our bodies react to this information, often involuntarily and without involvement of higher brain functions. And while the topography and cytoarchitecture of the human spinal cord is fairly well understood, the functional implications of some well-described structures remain elusive. Because of the central role the spinal cord plays in many forms of CNS impairment, a better understanding of the functional neuroanatomy of this structure is a prerequisite for addressing potential therapeutic approaches. This chapter gives an overview of spinal cord development, topography, cytoarchitecture, and functional assembly with a special focus on two aspects often compromised during spinal cord injury, namely, the control of micturition and the propriospinal neuron networks that hold great promise for the future improvement of therapies for patients suffering from spinal cord injury.

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2.1 The Anatomical Organization of the Spinal Cord

The spinal cord resides within the spinal canal of the vertebral column (Fig. 2.1) and, like the brain, is surrounded by cerebrospinal fluid and meninges. In the adult, the spinal cord extends from the foramen magnum to L1–L2. During development and up to 14 weeks post-conception (pc), the spinal cord covers the entire length of the embryo, with spinal nerves leaving the vertebral column through their corresponding intervertebral foramina. However, with subsequent growth and elongation of the vertebral column, a relative growth emerges (termed ascensus medullae): the vertebral column and its meninges extend faster than the actual spinal cord, so that in the adult, the caudal end of the spinal cord will eventually lie more rostral than the vertebral column. This final position explains the profoundly lengthened dorsal and ventral spinal roots, especially at the sacral end of the vertebral column (Fig. 2.1a). The distal end of the spinal cord is formed the conus medullaris (Fig. 2.1a, b), which is tethered to the bony spinal column via a terminal filum, a thread-like structure mostly composed of fibrous tissue.

A longitudinal fissure along the spinal cord is termed the ventral (anterior) median fissure (Fig. 2.1c). The spinal cord's ventral white commissure (Fig. 2.1c) forms its floor. The ventral median fissure has a corresponding counterpart at the

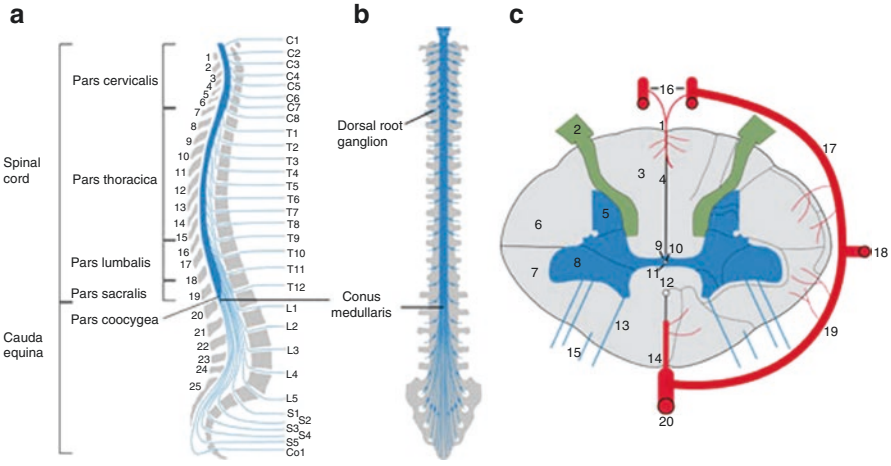

Fig. 2.1 The human vertebral column from (**a**) median-sagittal, (**b**) ventral, and (**c**) in a cross-sectional view of a cervical segment. Note the increasing shift between spinal segments and in the vertebrae. *1* posterior median sulcus, *2* dorsal horn, *3* dorsal column, *4* posterior median septum, *5* dorsal horn, *6* posterolateral column, *7* anterolateral column, *8* ventral horn, *9* posterior gray commissure, *10* central canal, *11* anterior gray commissure, *12* ventral (*white*) commissure, *13* anterior column, *14* anterior median fissure, *15* ventral root, *16* posterior spinal arteries, *17* posterior radicular artery, *18* lateral spinal artery, *19* anterior radicular artery, *20* anterior spinal artery (**c**) (adapted with permission from [79])

dorsal side, the shallower posterior (dorsal) median sulcus (Fig. 2.1c). From there, the posterior median septum, which is made up of pial tissue, extends to the central gray matter. A typical anatomical feature of spinal cord cross sections is the "butterfly-shaped" form of the central gray matter, which has two distinct regions, the dorsal and ventral horns (Fig. 2.1c). Of note, only in the thoracic and upper lumbar spinal cord, a third horn is visible, the (intermedio)lateral horn. This region contains neurons that belong to the autonomic nervous system. The thoracic lateral horn specifically contains preganglionic sympathetic neurons. Across all segments, the central connection of the gray matter (anterior gray commissure and intermediate gray matter, respectively [79, 120]), surrounds the central canal, which is lined by ependymal cells and contains cerebrospinal fluid.

The human spinal cord is subdivided into a total of 31 segments: 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, and 1 coccygeal (outlined in Fig. 2.1a). From each segment a pair of dorsal and ventral roots originates, which are composed of individual dorsal and ventral rootlets and together exit the spinal cord at the corresponding anterolateral and posterolateral depression, respectively. This point of exit (fila radicularia) is a continuity along the length of the spinal cord. The dorsal roots contain the dorsal root (spinal) ganglia, which are located within the intervertebral foramina (Fig. 2.1b). They are composed of pseudounipolar neurons, which give rise to a single axon with a bifurcation into a central and peripheral process. At the level of dorsal root ganglia, the dorsal and ventral roots of the spinal cord unite into a short spinal nerve. Of note, the nomenclature of spinal roots differs from the spinal canal segments. A segment is defined as the section of spinal cord from which a spinal nerve pair (left and right) extends toward the periphery. Consequently, the spinal cord segments do not necessarily correspond to those of the spinal canal due to the above-described developmental ascension of the spinal cord. As a consequence, the spinal roots have to descend further down to then exit the column at the appropriate intervertebral foramen (rostral for C1–C7 roots, caudal for all others). As a result, the definitive spinal cord ends at L1 with the conus medullaris (Fig. 2.1a, b), while the remaining bundle of lumbar, sacral, and coccygeal fibers further extend as the cauda equina down to Co1 (Fig. 2.1a, b).

2.1.1 Meninges of the Spinal Cord

As is typical for the CNS, three layers of meninges surround the spinal cord: (1) the superficial dura mater, (2) the arachnoid mater (intermediate), and (3) the inner pia mater. The pia mater is the origin of the denticulate ligament, an elastic structure that tethers the pia and the dura mater along the entire spinal cord. It is an essential part of the supporting structure for the cord in the spinal canal and provides stability. Three presumptive spaces appear within this sheathing of the spinal cord: the epidural, subdural, and subarachnoid space. Moving from the outside in, the epidural space is external of the dura mater and contains mostly loose connective tissue, epidural adipose tissue, the spinal nerve roots, and the internal vertebral venous plexus (see Sect. 2.1.2). In its rostrocaudal orientation, the epidural space

diminishes at the foramen magnum (here, the spinal dura mater merges with the endosteal dura of the cranium) and at the sacral hiatus. In the cervical and thoracic regions, the epidural space is filled with a large basivertebral vein.

Classic textbook anatomy highlights the subdural space as a true anatomical structure between the dura mater and arachnoid. However, as discussed by Watson and colleagues [120] based on data obtained by Reina, Vandenabeele, Haines, and others, this is most likely not the case [40, 94, 118]. This "space" is more likely a preparation artifact.

Finally, the subarachnoid space lies between the arachnoid and the pia mater. It contains cerebrospinal fluid and a loose network structure of collagen fibers and fibroblasts, the arachnoid trabeculae [40]. This trabecular structure connects the arachnoid to the pia mater and further contains leptomeningeal cells traversing the space and thus creating the so-called intermediate leptomeningeal layer, which closely resembles the cranial arachnoid trabecular network [76]. Overall, the subarachnoid space extends from the cranium down to the S2 vertebra. Functionally, the subarachnoidal space plays an important role for cerebrospinal fluid drainage [91], which is mostly accomplished by arachnoid villi extending into the subarachnoid space.

2.1.2 Vasculature of the Spinal Cord

Apart from the usual functional aspects of gas and nutrient exchange, blood flow in the CNS is fundamentally important for clearance of metabolic heat. Thus, it is only logical that during embryonic development, angiogenesis and neurogenesis go hand in hand, supporting each other also by using similar signaling pathways [102, 113]. Examples of growth factors that support both angiogenesis and neurogenesis include vascular endothelial growth factor (VEGF), members of the fibroblast growth factor (FGF) family, and brain-derived neurotrophic factor (BDNF), among others (reviewed in [93]).

2.1.2.1 Arteries

The main arterial supply of the spinal cord is provided by posterior (dorsal), lateral, and anterior (ventral) vessels that span the entire cord length (Fig. 2.1c, see also [120]). The anterior spinal artery is located directly at the indentation of the anterior median fissure (Fig. 2.1c). In contrast, two posterior spinal arteries are located just ventral of the dorsal root entrance to the spinal cord, and the lateral spinal arteries can be observed somewhat halfway between the dorsal and ventral roots (Fig. 2.1c). Various transverse arteries extend from this arterial transverse anastomotic circle into the spinal cord and predominantly branch in the gray matter. The origin can be variable, but usually the anterior spinal artery is a derivate of two branches of the vertebral arteries at the level of the pyramidal decussation. The posterior spinal arteries either derive directly from the vertebral artery in the neck region or stem from the posterior inferior cerebellar artery. The posterior spinal arteries also receive blood from segmental arteries (ascending cervical artery, profound cervical artery, posterior intercostal artery, and lumbar arteries). The most

prominent supporting artery is the artery of Adamkiewicz, which supplies the thoracolumbar and sacral spinal cord. In most cases it originates from the abdominal aorta approximately at T9, traverses the intervertebral foramen, and eventually anastomoses with the anterior spinal artery. Radicular arteries enter the spinal canal alongside the spinal nerves in the intervertebral foramina, then branch outside the dura mater, and follow the dorsal and ventral roots, respectively, to enter the spinal cord (Fig. 2.1c). Within the gray and white matter of the spinal cord, an intricate capillary network is formed and is significantly more elaborated in the gray matter. It was discovered in the mid-1940s that this imbalance of microvascularization mostly correlates with the number and density of synapses with high levels of mitochondria, of which there are many more in the gray than white matter [103]. Furthermore, some regions also seem to contain more capillaries than others, for example, the corticospinal tract contains about twice the amount of capillaries than the cuneate fasciculus [129].

2.1.2.2 Veins

Along the surface of the spinal cord, an elaborate venous plexus can be observed. Similar to the arterial layout, an anterior and posterior spinal vein spans the longitudinal axis of the spinal cord but can show significant caliber variations. Both the anterior and posterior veins anastomose via a network of smaller veins that circumvent the spinal cord. Especially at the cervical and lumbar enlargements, where the majority of spinal nerves innervating the extremities exit the cord, a larger venous transverse anastomotic circle can be found.

2.2 Development of the Spinal Cord

2.2.1 The Neural Plate and Neural Tube

The first significant step during vertebrate nervous system development is the achievement of neural identity from dorsal ectodermal cells positioned along the midline of the gastrulating embryo. Subsequently, the neural plate will form and, along its two major axes (anterior-posterior and dorsal-ventral), it supports the generation of all neural cell types that will ultimately shape the mature CNS.

The CNS derives entirely from ectoderm. Its earliest derivatives include the neural plate and the neural crest. The neural plate is a somewhat oval-shaped region with elevated epithelial cells rostral to the primitive pit (Fig. 2.2a). Beginning with Carnegie stage 6 (day 18pc), the neural plate can be distinguished from the surrounding ectoderm in the anterior germinal disc and is wider there than at its caudal end. The neural crest and the embryo's placodes develop in a band of cells directly adjacent to the neural plate. These cells are in direct contact with the surrounding epidermal ectoderm.

The neural plate is induced due to an inhibition of epidermis formation, which in turn is driven by signals that derive from the primitive node at the cranial end of the embryo (Fig. 2.2a), [101]. Within 24 h of the first appearance of the neural plate,

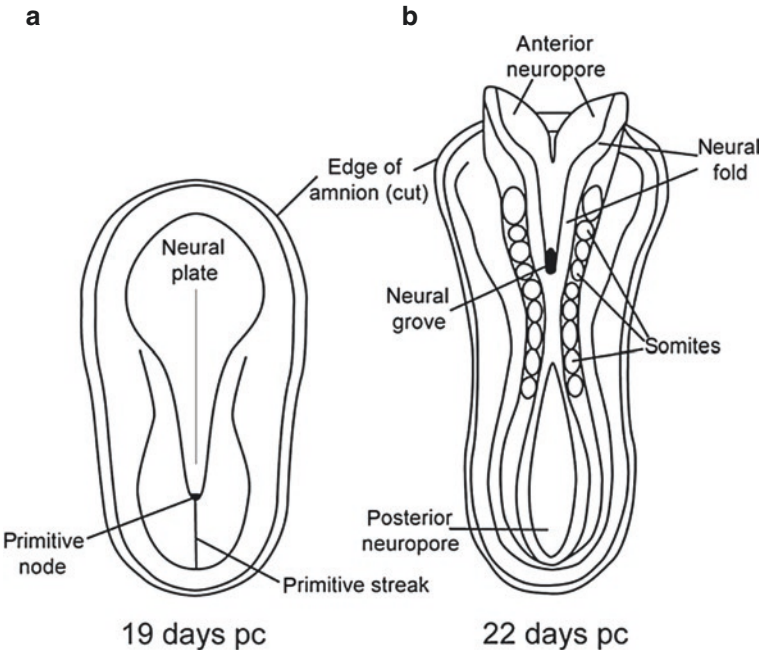

Fig. 2.2 Embryonic development of the (**a**) neural plate and (**b**) neural tube, dorsal view. At Carnegie stage 6 (day 18pc), the neural plate can be distinguished from the surrounding ectoderm and is induced due to an inhibition of epidermis formation, which in turn is driven by signals that derive from the primitive node. Within 24 h of the first appearance of the neural plate, folds appear at its respective edges, thereby creating the neural fold along the midline. At Carnegie stage 9 (20 days pc), fusion of the opposing neural folds and subsequent formation of the neural tube occurs at the hindbrain – spinal cord junction. The two open ends after neural fold closure are the neuropores. They remain temporarily open (modified from [101, 120])

folds appear at its respective edges, thereby creating the neural fold along the embryo's midline (Fig. 2.2a, b).

Several factors contribute to the complex event of axial patterning and neurulation – the latter describing the event of embryonic folding not only along the midline but also in a dorsoventral orientation to ultimately close and form the neural tube. Cell intercalation into the embryonic midline results in a narrowing along the medial-lateral axis (convergence) and simultaneous rostrocaudal lengthening (extension) [50]. Specifically, the caudalizing event is driven by signaling molecules of the fibroblast growth factor (FGF) family, while the rostralizing event relies heavily on retinoic acid signals [56].

The other directional folding event along the dorsoventral axis is carried by bone morphogenic proteins (BMPs) for the dorsalizing orientation and sonic hedgehog (SHH) for the major ventralizing factor of this event [127]. Both factors significantly contribute to so-called hinge point (HP) formation [108]. Median and dorsolateral HPs are required for correct neural tube folding and closure, and lack of correct signaling results in the emergence of a number of neural tube closure defects along the embryo, which, depending on the position of the defect, can range from

anencephaly to craniorachischisis, lumbosacral spina bifida, or spinal dysraphism and encephalocele [18, 37].

In humans, the next major time point in the development of the spinal cord is at around Carnegie stage 9 (20 days pc). Here, fusion of the opposing neural folds and subsequent formation of the neural tube occur at the hindbrain – spinal cord junction. This event requires several days to be completed and is coordinated simultaneously both at the rostral and caudal ends [82]. After closure of the neural folds, both ends temporarily remain open and are referred to as neuropores (Fig. 2.2b). When by 28 days pc both neuropores have been closed, the rostral neural tube initiates brain vesicle development, while the caudal pore is triggered to form the primitive spinal cord. This process of neural tube closure and extension of the spinal cord to S4/S5 is termed primary neurulation, with the secondary neurulation describing the event during which more caudal levels of the spinal cord are generated via connection and fusion of mesodermal cells. These cells then epithelize and subsequently merge with the rest of the tube [101].

2.2.2 Derivatives of the Neural Crest

Cells that emerge along the edge of the neural folds during the above-described process form what is termed the neural crest. They reside along the entire length of the neural tube, and while those that migrate along a dorsolateral pathway give rise to a number of neural cell populations later in life, those that transform into sensory ganglia are of distinct significance for spinal cord development: they are the origin of all dorsal root ganglia (DRG). Morphologically, the somata of these neurons remain in place, but the cells project a peripheral process to innervate somatic or visceral regions, while a central projection extends into the forming dorsal horn of the spinal cord. The extension of the peripheral projections heavily depends on appropriate trophic factor-mediated guidance and survival cues provided by the respective target sites. At the same time, a solid balance with repulsion events contributes to process pathfinding. The notochord, ventral spinal cord, and dermomyotome of the developing embryo have putative chemorepulsive effects on the extending peripheral DRG processes. Masuda and Shiga suggested members of the semaphorin family along with chondroitin sulfate proteoglycans be included among factors secreted by the notochord and dermomyotome, respectively, while the chemorepulsive carriers secreted by the ventral spine remain elusive [61].

2.2.3 Derivatives of the Alar and Basal Plates

A fundamental step during spinal cord development is the formation of the regions that will later form sensory and motor areas, respectively. A cross section through a 6-week-old human embryo is depicted in Fig. 2.3. Here, the roof and floor plates as well as a ventricular zone of the developing embryo are separated clearly. They are surrounded by neuroepithelial cells that produce a pseudostratified wall to the neural tube lumen. In this region, a number of cells with similar fates come to lie close to each other and ultimately perform cell-type-specific coupling, which depends on

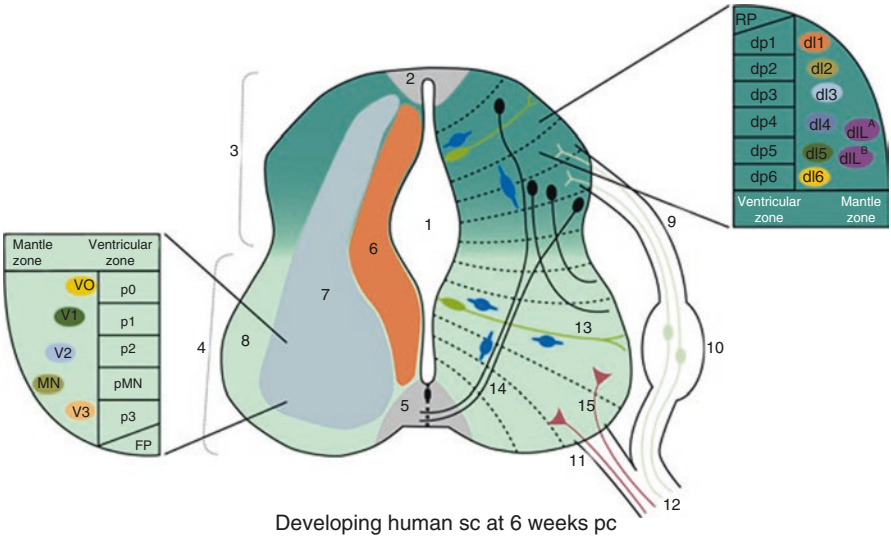

Fig. 2.3 Cell type specification and migratory paths in the human spinal cord. At around 6 weeks of age, progenitor domains and daughter cells have been specified (inserts for basal and roof plate). In the ventral spinal cord (basal plate insert, left), five progenitor pools in the ventricular zone (p0–p3, pMN) give rise to five mature neuron populations in the mantle zone (V0–V3, MN). In the dorsal spinal cord (alar plate insert, right), six progenitor domains (dp1–dp6) give rise to six early-born interneurons (dI1–dI6) and two late-born interneurons (dIL^A, dIL^B). Cells and processes in the center graphic depict migratory routes of neuroblasts (see text for details). *1* spinal canal, *2* roof plate, *3* alar plate, *4* basal plate, *5* floor plate, *6* matrix zone, *7* mantle zone (later *gray* matter), *8* marginal zone (later *white* matter), *9* dorsal root, *10* dorsal root ganglion, *11* ventral root, *12* spinal nerve, *13* ependymal cell (guides radial migration of neuroblasts), *14* arcuate fibers (guide tangential migration of neuroblasts), *15* motoneurons, *FP* floor plate, *RP* roof plate (adapted from [79, 133])

both chemical and bioelectrical signaling [1, 8], thus building the mantle layer between the ventricular zone and the marginal zone. The mantle layer, which resides around the primitive spinal cord, arises from multiple neuroepithelial cell divisions. These then lead to the subsequent emergence of primitive nerve cells and the accumulation of postmitotic neuroblasts beneath the external limiting membrane of the neural tube. The mantle layer will become the gray matter of the spinal cord. In turn, the marginal zone will ultimately become the white matter of the mature spinal cord.

Within the mantle layer, two distinct, paired regions can be observed: the dorsal thickening is referred to as the alar plate (future sensory areas of the spinal cord) and the ventral thickening is the basal plate (future motor areas of the spinal cord). Notably, the cells that reside outside of the roof and floor plates will ultimately serve as dorsal and ventral white commissures that facilitate the crossing of axons in the mature spinal cord.

In terms of cellular derivatives, the alar and basal plates and their induction to produce the cell types of the spinal cord have been investigated mostly in animal

models. However, it is reasonable to assume similar mechanisms for human spinal cord development, as many of the signaling molecules and guidance factors along with their gene regulation are highly conserved among vertebrate species. While the roof plate is most likely initiated by signaling from the overlying ectoderm [16, 59], the floor plate is induced by axial mesoderm [2, 72]. Once established, the floor plate has been shown to generate a SHH gradient, which in turn induces the production of distinct pools of progenitors in the neuroepithelial ventricular zone ([13, 133], Fig. 2.3 left panel). Likewise, the roof plate and its external ectoderm, by generating a BMP gradient that is also reciprocal to the floor plate's SHH gradient, produces six progenitor domains, which in turn generate six distinct early-born and two late-born dorsal interneuron cell populations [133] (Fig. 2.3 right panel). Like in the developing brain, the majority of neuroblasts use migration paths along radial glia cells to leave the matrix zone and reach the mantle zone (Fig. 2.3). However, not all neuroblasts follow this radial migration pattern. A subset of neuroblasts has been observed to migrate tangentially. For example, axons of some early-differentiating alar plate-derived neurons extend toward the ventral spinal cord and intersect in the floor plate. These arcuate fibers build a pathway, the so-called circumferential pathway [42], which in various species serves as both a dorsal-to-ventral [54] and ventral-to-dorsal migration path for neuroblasts [87]. Thus, it provides important commissural axon corridors that are essential for correct target innervation.

2.2.4 Cell Type Specification of the Spinal Cord

2.2.4.1 Motoneurons

All motoneurons originate from a single ventral progenitor domain (Fig. 2.3, left panel), yet strikingly, their delicate specification later allows for the coordinated movement of the large variety of muscles in the human body. For this, the positional identity of motoneurons along the spinal cord's rostral-caudal axis is key. This position and location identity is the direct result of the concerted action of multiple signaling molecules (for review see [21, 107]).

These spatiotemporal signaling events lead to different birthdates of motoneuron populations. Early-born motoneurons migrate into the basal plate while trailing a radially oriented process that has a distinct central orientation, already aiming at its target region. Next, the emerging motoneuron develops an early axonal domain, which is distinguishable from the cell's somatodendritic domain by expression of early axon-specific markers such as scaffolding proteins for the evolving axon initial segment [53]. Finally, the axons will traverse the marginal zone and emerge from the ventral surface of the cord, thus forming the ventral roots of the spinal cord. Likewise, dendrites will branch into the newly forming neuropil of the ventral horn and gray matter.

Ventral horn neurons arise from five distinct columnar subpopulations, of which four are interneuronal and one is motoneuronal (Fig. 2.3, left panel). The latter will produce three columns of neurons: (1) lateral motoneurons positioned at the

cervical and lumbosacral enlargement of the spinal cord will later innervate the musculature of the extremities, (2) medial motoneurons that can be found throughout the entire spinal cord will later innervate axial muscles, and (3) visceral motoneurons that arise from an intermediolateral column in the thoracic and cranial lumbar segments. At 8–10 weeks pc in humans, motoneurons will segregate into specific somatic motor columns, a process which depends both on genetic and epigenetic regulation [19]. Francius and Clotman most recently published a comprehensive review on motoneuron specification and diversity [34].

As already mentioned above, target-finding and long-term survival of motoneurons depends predominantly on specific guidance- and survival cues. In this context, far more motoneurons are produced than will ultimately survive and innervate target sites. Several signaling molecule families are involved in this important elimination event, for example, classic neurotrophins (BDNF, NT3, NT4), several members of the cytokine family (ciliary-derived neurotrophic factor (CNTF), leukemia inhibitory factor (LIF), cardiotropin-1), several TGF-β family members (glial-derived neurotrophic factor (GDNF), neurturin, artemin, persephin), insulin-like growth factors IGF-I and IGF-II, and members of the fibroblast growth factor family (FGF-1, FGF-2, and FGF-5) (for review see [58, 106]).

2.2.4.2 Interneurons

Interneurons are born both in the areas composed of, and directly adjacent to, the dorsal roof plate as well as the ventral floor plate (Fig. 2.3). The dorsal spinal cord establishes six distinct progenitor pools (dp1–dp6), which in turn give rise to six early-born (dI1–dI6) and two late-born interneuronal subtypes (dIL^A and dIL^B) that differ by birthdate, relative dorsoventral position, and gene expression profiles [133]. Interneurons in the ventricular zone close to the floor plate emerge from the above mentioned four progenitor domains p0–p03 that result in mature interneuronal subtypes V0–V3 (Fig. 2.3, also refer to Sect. 2.5.3.1). Interestingly, many of these early subtypes have been found to develop into commissural interneurons projecting to the contralateral side of the spinal cord. In the mature CNS, these commissural interneurons are essential for left-right locomotor coordination and represent a major component of central pattern generators (CPGs) that play a fundamental role for the rhythmic, coordinated movement of limbs and trunk [117]. CPGs will be discussed in more detail in Sect. 2.5. It is important to keep in mind that while the nomenclature for interneuron subtypes may seem simple with four major ventral classes V0–V3 and six dorsal classes, respectively, recent data actually identified several subsets within each class depending on the expression of specific sets of transcription factors [35].

2.2.4.3 Glia

Glial subtypes of the early spinal cord include radial glia, oligodendrocytes, astrocytes, and ependymal cells. Generally, gliogenesis occurs after the brief phase of neurogenesis, and astrocytes, which develop in large parts from radial glia [6, 64], emerge before oligodendrocytes, which later are the sole source for CNS myelin. Notably, in humans, oligodendrocyte precursors first reside in the ventral

ventricular zone close to the floor plate and in the direct neighborhood of a motoneuron domain [41]. In fact, data from genetic studies suggest that oligodendrocytes and motoneurons share a common ancestral progenitor [60, 109]. In contrast, ventral interneurons seem to share a common ancestor with different astrocyte subtypes that ultimately settle in various gray and white matter areas depending on their origin [97, 115]. Oligodendrocytes are sequentially produced in three distinct waves. First, ventral precursors from the motoneuron domain arise and migrate along the entire neural tube. As with motoneuron specification, the development of these cells is SHH mediated and is repressed by dorsally secreted BMPs and WNT proteins. The second wave occurs later in the fetal phase. Here, progenitors located in the dorsal spinal cord develop from dp3–dp6 interneuron domains. Finally, the third wave is characteristically initiated after birth. The origin of these cells remains elusive [70, 97].

Ependymal cells eventually come to line the central canal of the spinal cord but are absent from other spinal structures. They guide radially migrating neuroblasts during development (Fig. 2.3). Last but not least, microglia appear in the human spinal cord around 9 weeks pc and undergo major infiltration of the tissues from 16 weeks pc on [96]. They most likely colonize the developing spinal cord along with the emerging vascularization of the tissue [96].

2.2.5 Emergence of Ascending and Descending Spinal Tracts

The earliest time point at which discernible ascending (spinocerebellar) neurons appear in humans is 10 weeks pc [17]. In a similar time window, by 13 weeks pc, the lateral corticospinal tract in humans has reached the caudal medulla oblongata. Just 2 weeks later, the pyramidal decussation is completed (reviewed in [112]). Next, the cervical spinal cord is reached between 14 and 16 weeks pc, and then a brief stop in further progression can be observed. The corticospinal tract invades the more caudal regions of the spinal cord at a later stage of development: 17 weeks pc for the low thoracic spinal cord, 27 weeks pc for the lumbosacral spinal cord. The early contact between descending axons of the corticospinal tract and corresponding synaptic targets in the spinal cord represents an important event for proper structural and functional maturation of the spinal cord. The maturation of spinal motor centers requires neuronal activity provided by the aforementioned contact [31]. This activity-dependent pattern for correct tract formation is especially important, considering that the developmental hallmark of initial exuberant axonal growth with subsequent substantial axon loss depends largely on neuronal activity and growth factors (whose expression can also be activity dependent). Hence, descending inputs are essential for the induction of plasticity and appropriate circuit formation [110]. In fact, recent data suggest that different motor systems can interact during development to drive each other's adult specification [123]. The authors suggest that the developing rubrospinal system is under activity-dependent regulation by the corticospinal system for establishing mature rubrospinal connections and a corresponding red nucleus motor map.

2.2.6 Myelination of Spinal Cord Tracts

Contrary to many mammals where myelination is part of the postnatal developmental period, first myelination of axons in the human can be observed in the early fetal spinal cord (e.g., less than 16 weeks pc shown by [78]). However, the majority of myelination cannot be seen until the second trimester. A distinct temporal order of myelinating events has been described previously. The earliest structure to myelinate is the medial longitudinal fasciculus (20 weeks pc), with the corticospinal tract being the last, still undergoing myelination at birth [121]. The same authors also described a spatiotemporal gradient of myelination, in which the three major protein classes myelin basic protein (MBP), proteolipid protein (PLP), and myelin-associated glycoprotein (MAG) appear along an anteroposterior and rostrocaudal gradient, with MBP emerging first. On a molecular level, oligodendrocyte progenitors – after migration and arrival at the correct location – undergo terminal differentiation into so-called premyelinating oligodendrocytes. This event follows a rostrocaudal gradient in the spinal cord [11]. Their terminal differentiation then includes the actual process of myelination, which requires physical contact to the axon that is to be myelinated. Again all these steps underlie intricate molecular regulation that depends on a number of developmental genes and factors (for a detailed review, see [70]).

2.3 Cytoarchitecture and Pathways of the Spinal Cord

2.3.1 Spinal Cord Gray Matter

Based on a fundamental anatomical nomenclature for the cat spinal cord gray matter first published by Rexed [95], a similar laminar cytoarchitecture of the gray matter also applies to humans [105]. An overview is provided in Table 2.1. The dorsal horn includes laminae I–VI, while laminae V–X reside in the base of the dorsal horn and the central region of the ventral horn (Fig. 2.4). However, not all laminae can be clearly distinguished from each other. Laminae I–VIII span the entire length of the spinal cord, although their size can vary significantly from one segment to the next. Of note, lamina IX cannot be understood as one section in the classical sense, but rather as motoneuron pools interspersed within laminae VII and VIII (Fig. 2.4).

Lamina I (zona marginalis, substantia spongiosa) has a reticular appearance and is composed of predominantly fusiform neurons (marginal cells). It borders with the tract of Lissauer, the region, where the dorsal horn contacts the pial surface of the spinal cord. It is visible as a band of unmyelinated or sparely myelinated afferent fibers also known as the posterolateral tract and contains axons projecting toward central regions, carrying nociceptive and thermoreceptive information. Neurons in lamina I are important for nociception and thermoreception and are the principal site for termination of nociceptive afferents. They use mainly glutamate, substance P, and calcitonin gene-related peptide (CGRP) as well as other peptides as transmitters. Lamina I neurons can also respond to mechanical stimulation from Aβ-fibers

Table 2.1 Laminae and nuclei of the spinal cord

Region	Nuclei	Laminae
Dorsal horn	Marginal zone	I
	Substantia gelatinosa	II
	Nucleus proprius	III, IV
	Neck of dorsal horn	V
	Base of dorsal horn	VI
Intermediate zone	Stilling-Clarke's nucleus, intermediolateral nucleus	VII
Ventral horn	Commissural nucleus	VIII
	Motor nuclei	IX
Gray matter around central canal	Grisea centralis	X

modified from [9]

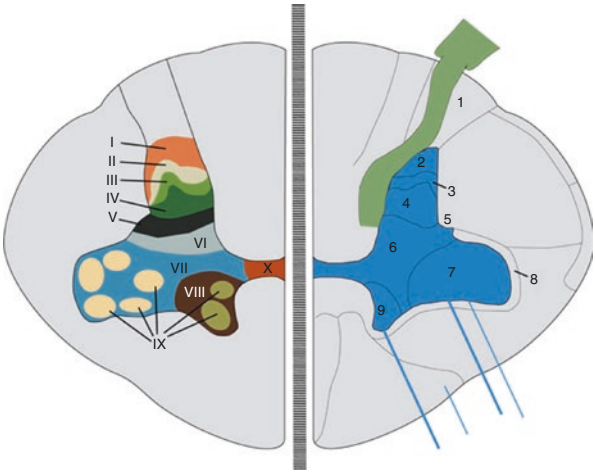

Fig. 2.4 Cytoarchitecture of the spinal cord gray matter. *Left side*: Lamina of the *gray* matter after the nomenclature of Rexed indicated by roman numerals (laminae *I* through *X*). *Right side*: *1* tract of Lissauer, *2* marginal cells (lamina *I*), *3* substantia gelatinosa (laminae *II+III*), *4* nucleus proprius (lamina *IV*), *5* intermediate zone, *6* intermediate zone (laminae *V–VIII*), *7* lateral motor column (lamina *IX*), *8* ground bundles (fasciculi proprii), *9* medial motor column (lamina *IX*), *10* ventral root (modified with permission from [79])

[124]. Interneurons in lamina I modulate nociception and signal predominantly via opioids, γ-aminobutyric acid (GABA), and glycine.

Like lamina I, lamina II (substantia gelatinosa) is a major nociceptive transmission and computation center and principal site for termination of Aδ- and C-fibers. It is composed of a great number of smaller, densely packed neurons and many

unmyelinated axons. Neurons in lamina II form mostly local connections, with terminal axon collaterals reaching from lamina III as deep as lamina V [55]. Lamina II neurons function mostly as interneurons, and an estimated third of these contain GABA and glycine [114]. Other neurotransmitters in lamina II interneurons include CGRP, substance P, and vasoactive intestinal polypeptide (VIP).

Neurons in laminae III and IV (nucleus proprius) are larger and less densely packed than in laminae I and II due to numerous myelinated axons that traverse this lamina. Again, a large portion of neurons here are interneurons, with dendrites that extend mostly rostrocaudally. Transmitter types include GABA, glycine, dopamine, and substance P, among others. Functionally, some neurons seem to respond to fine tactile information, while others respond to rather strong, coarse pressure application. In the upper cervical segments, the medial region of lamina IV builds the internal basilar nucleus, a caudal extension of the cuneate nucleus [7].

Lamina V is the site of convergence between somatic and visceral input. It can be further divided into a medial part (ascending projection neurons) and a lateral part (preganglionic neurons in the lateral horn). The latter contains large somata, intercalated with thick myelinated axon tracts. In the human, this lamina cannot be clearly separated from lamina VI [104]. Dendrites in lamina V extend mostly in a dorsoventral orientation and can reach into laminae II and VII, respectively. Neurons in lamina V receive afferent input from the skin, musculature, and visceral organs with mixed modalities (mechanosensory, nociceptive, chemoreceptive). The major neurotransmitters present are GABA, dopamine, glycine, and substance P, among others.

Lamina VI is the deepest layer of the dorsal horn. As mentioned before, this lamina is almost indistinguishable from laminae V and VII, only visible in the cervical and lumbar enlargements. Similar to lamina V, it is also divided into a medial and lateral zone. Afferent input comes from collaterals of Aα-fibers (from muscle spindles). Lamina VI also receives input from cutaneous and nociceptive fibers. The majority of lamina VI neurons are either propriospinal neurons or interneurons. The latter are more local in their projection, many of them innervating ventral horn motoneurons. Hence, the major function of lamina VI interneurons seems to be the control of reflex pathways.

Lamina VII comprises most of the intermediate zone. The cell population in lamina VII is evenly sized and spaced, and the majority of cells are premotor interneurons projecting to the large motoneurons of lamina IX. In fact, lamina VII is a motor computation hub in that descending motor pathways control spinal motoneurons by synaptic transmission via interneurons in lamina VII. It is assumed that lamina VII interneurons are typically prewired to execute all aspects of a voluntary movement [120]. The modular arrangement of these interneuron-to-motoneuron connections thus provides a very potent way for the brain to execute directed voluntary movements. Indeed, the topographical arrangement of motoneuron columns matches the distribution of interneurons in lamina VII, with those modulating proximal musculature being placed more medial, and those driving distal movements being located more laterally.

Lamina VII contains three distinct nuclei: (1) the nucleus dorsalis (Stilling-Clarke, (C8) T1–L2/L3; see Sect. 2.4), with afferent innervation from proprioceptive fibers from muscles and joints; (2) the central cervical nucleus (C1–C4), with afferent input from the head and neck musculature, the vertebral joints, and the vestibular nuclei, which all coordinate head and neck movement; and (3) the intermediomedial nucleus (T1–L3), a part of the autonomic cell columns in lamina VII (cholinergic neurons). The latter are interconnected with sympathetic cells from the intermediolateral nucleus (lateral in C8–L3). These cells are preganglionic, visceroefferent neurons of the sympathetic and parasympathetic systems with input from supraspinal centers in the hypothalamus, pons, and medulla oblongata. Importantly, these nuclei also receive afferent visceral input. Both the intermediolateral and medial nuclei are connected with each other and with the contralateral side. Also located in lamina VII (lateral part) are the parasympathetic sacral nuclei (S2–S4), whose neurons innervate the large intestine, the urethral and anal sphincter, the reproductive organs, and the urinary bladder (see Sect. 2.4).

Neurons in lamina VIII are heterogeneous in size and shape at different levels along the spinal cord and their dendrites project mostly in the dorsoventral orientation. Dorsal dendrites, while not crossing the midline, are extended toward lamina VII and the ventral gray commissure. The majority of cells are GABAergic with input from propriospinal afferents and from supraspinal, vestibular, and reticulospinal afferents. Neurons of lamina VIII have a central role in the coordination of motor activity. For example, the left-right coordination of movement seems to be controlled by lamina VIII neurons [80]. Also, the majority of neurons with projections in the long propriospinal pathways that connect the lumbar and cervical enlargements are located in lamina VII, and they play a fundamental role for the coordination of front and hind limb movement [120]. Further details are discussed in Sect. 2.5.

Lamina IX is not a true lamina, but a set of columns in laminae VII and VIII and along the edge of X. It is the major site for large α-motoneurons (innervate striate musculature) and smaller γ-motoneurons (innervate muscle spindles) in the spinal cord. They are surrounded by a specific class of interneurons, so-called Renshaw cells, which provide recurrent inhibition for motoneurons and thus build an essential negative feedback mechanism for motoneuron activity. Motoneurons in lamina IX are organized in columns, which differ in size and number depending on the segmental level. Generally, four distinct columns are separated:

1. Medial group: Innervation of axial musculature; divided into the anteromedial nucleus (C1–Co1) and posteromedial nucleus (C1, T1–L2).
2. Lateral group: Innervation of intercostal and peritoneal wall musculature; clear differentiation into separate nuclei in the region of the cervical and lumbar enlargements with the anterior and anterolateral nuclei (C5–C8, L2–S1), the posterolateral nucleus (C5–C8, L2–S2), and the retroposterolateral nucleus (C8–T1, S1–S3). These innervate the musculature of the extremities.
3. Central group: Only visible in specific segments. From C3–C5, contains the nucleus of the phrenic nerve (innervation of the diaphragm); from C1–C5, contains the nucleus of the accessory nerve (ultimately becomes one origin of the accessory

nerve after exiting the spinal cord and ascending in the subarachnoidal space through the foramen magnum).
4. Onuf's nucleus: In S1–S3, with motoneurons of the pudendal nerve, innervates the striate muscles of the urethra sphincter and rectum.

Lamina X (central gray of the spinal cord) extends along the entire spinal cord and encompasses the region around the central canal. Neurons in this lamina are smaller than those from the surrounding lamina VII and are more densely packed. Neurons of the central autonomic area are located here. Cells in lamina X receive input from C-fibers and Aδ-fibers of both somatic and visceral origin. Likewise, lamina X functions in both nociception and viscerоception (including visceral pain and mechanoreception). Axons from lamina X project into laminae V, VI, and VII, among other targets in central regions of the brain.

2.3.2 Spinal Cord White Matter

As outlined in Sect. 2.1, the horns of the gray matter divide the surrounding white matter into three columns: a dorsal (posterior), a lateral, and a ventral (anterior). Yet boundaries between these parts are not necessarily distinct and clear. Within the white matter, ascending and descending pathways are distinguished from each other and will be discussed in the following sections (summarized in Table 2.2).

Overall, the ascending and descending tracts can be subdivided further into functional groups (Figs. 2.5 and 2.6). In the ascending orientation, we find (1) the posterior column-medial lemniscal system, which relays sensory information on vibration, proprioception, and fine touch (via the cuneate and gracile fasciculus), (2) the anterolateral system, which transmits nociceptive, thermoreceptive, and crude touch information (via the anterior and lateral spinothalamic tracts, spinoreticular tract, etc.), and (3) the cerebellar input system, which is responsible for proprioceptive sensibility of the upper and lower limbs (composed of the dorsal spinocerebellar tract, cuneocerebellar tract, and smaller tracts such as ventral and rostral spinocerebellar tracts).

The descending pathways are grouped into (4) the lateral motor system for the movement of contralateral limbs (via the lateral corticospinal tract, rubrospinal tract) and (5) the medial motor system, which is responsible for control of bilateral trunk muscles, head/neck positioning, balance, and other posture and gait-related movements (via the anterior corticospinal tract, the medial and lateral vestibulospinal tracts, the reticulospinal tract, and the tectospinal tract).

2.3.2.1 The Main Ascending (Somatosensory) Pathways

As outlined below, two major systems, the posterior column-medial lemniscal pathway and the anterolateral system, compose the ascending system and convey somatosensory information to the brain (Figs. 2.5 and 2.6). Sensory neurons, which transmit information from the periphery to the spinal cord, are classified according to their axon diameter and hence, conduction velocities. They include 1) myelinated Aα-fibers for proprioception (receptors are Golgi tendon organs and muscle

Table 2.2 Summary of the most important ascending and descending long tracts of the spinal cord

System/pathway	Origin	Decussation	Level of termination	Function
Posterior column-medial lemniscal pathways				
Cuneate fasciculus	Peripheral afferents, above T6	Uncrossed	Ipsilateral cuneate nucleus	Proprioception, vibration sense, fine touch
Gracile fasciculus	Peripheral afferents, legs, and lower trunk	Uncrossed	Ipsilateral gracile nucleus	Proprioception, vibration sense, fine touch
Anterolateral system				
Spinothalamic tract (lateral and anterior)	Especially laminae I–II, also V	Ventral commissure of the spinal cord at the level of the originating segment	Mostly VPL of the thalamus	Discriminative aspects of nociception + thermoreception (location, intensity), tactile input (nondiscriminative)
Spinoreticular tract (sometimes seen as part of spinothalamic tract)	Laminae VI–VIII	Predominantly ipsilateral, some fibers in anterior white commissure	Medullary-pontine reticular formation with projection to intralaminar thalamic nuclei	Emotional + arousal aspects of nociception
Spinomesencephalic tract	Laminae I and V	Anterior white commissure	Periaqueductal gray (midbrain), superior colliculus, midbrain raphe nuclei, parabrachial nucleus	Emotional component of nociception
Spinotectal tract	Laminae I and V	Anterior white commissure	Deep layers of superior colliculus	Reflex reaction after nociceptive stimuli (turning of eyes/head/upper body toward stimulus)
Spinohypothalamic tract	Lamina II	Anterior white commissure	Hypothalamus	Autonomic + reflex responses (e.g., endocrine, cardiovascular), nociceptive input

(continued)

Table 2.2 (continued)

System/pathway	Origin	Decussation	Level of termination	Function
Cerebellar input system				
Cuneocerebellar tract	Accessory or lateral cuneate nucleus (input from C2–T5)	Uncrossed	Ipsilateral anterior lobe of cerebellum via restiform body	Proprioceptive input from ipsilateral neck + upper limb
Rostral spinocerebellar tract	Dorsal horn (C4–C8), lamina VII	Uncrossed	Cerebellum	Proprioceptive input from ipsilateral head + upper limb
Dorsal (posterior) spinocerebellar tract	Dorsal nucleus of Clarke (C8–L2/L3), lamina VII	Uncrossed	Ipsilateral cerebellar vermis	Proprioceptive input from ipsilateral lower trunk + lower limbs
Ventral (anterior) spinocerebellar tract	Dorsal horn; laminae V–VII of L, S, and Co levels; L3–L5 anterolateral border of anterior horn (spinal border cells)	Anterior white commissure, then back to ipsilateral in the superior cerebellar peduncle	Ipsilateral cerebellar vermis	Proprioceptive input from ipsilateral lower trunk + lower limbs
Lateral motor system				
Lateral corticospinal tract	Primary motor cortex, other frontal, parietal regions	Pyramidal decussation (cervicomedullary junction)	Entire cord (cervical and lumbar enlargements)	Movement of contralateral limbs
Rubrospinal tract	Nucleus ruber (magnocellular)	Ventral tegmental decussation (midbrain)	Cervical segments of the cord	Movement of contralateral upper limbs (flexor muscles)
Medial motor system				
Anterior corticospinal tract	Primary motor cortex, supplementary motor area	Anterior white commissure	Cervical, upper thoracic segments of the cord	Control of biaxial and girdle musculature

Vestibulospinal tract (VST)	Medial VST: medial and inferior vestibular nuclei; lateral VST: lateral vestibular nucleus	Bilateral Ipsilateral	Medial VST: cervical, upper thoracic cord; lateral VST: entire cord	Antigravity muscles, Medial VST: head/neck positioning; lateral VST: balance
Reticulospinal tracts	Pontine and medullary reticular formation, medial + lateral	Uncrossed	Entire cord, laminae VII + VIII (medial) and VII + IX (lateral)	Maintenance of posture, gait-related movements, modulation of muscle tone
Tectospinal tract	Superior colliculus	Dorsal tegmental decussation (midbrain)	Cervical cord	Head/eye coordination (uncertain in humans)

adapted from [9, 84]

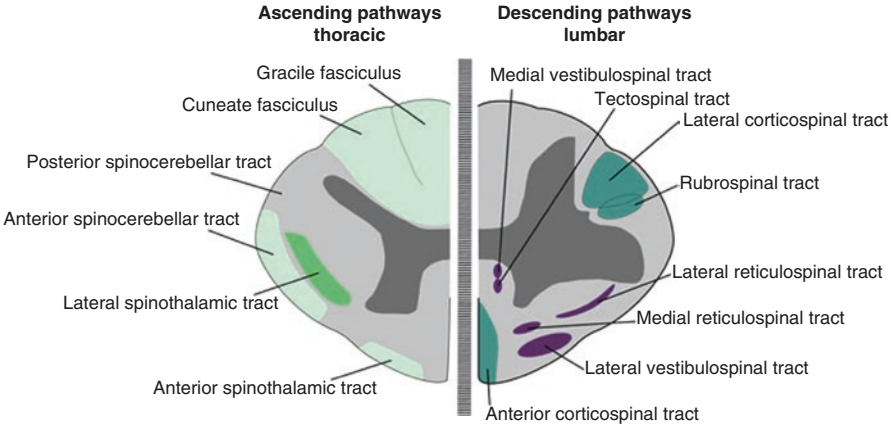

Fig. 2.5 The ascending (sensory) and descending (motor) pathways of the spinal cord. The image summarizes the major pathways discussed in Sect. 2.3 and outlined in Table 2.2

spindles), 2) myelinated Aß-fibers also for proprioception (receptors are muscle spindles, Meissner's corpuscles (superficial touch), Merkel receptors (superficial touch), Pacinian corpuscles (vibration), Ruffini endings (stretch), and hair follicle receptors (touch, vibration)), 3) scarcely myelinated Aδ-fibers for itch, nociception, and cold thermoreception (intraepidermal nerve fibers), and 4) unmyelinated C-fibers for itch, nociception, and warm thermoreception (intraepidermal nerve fibers). Somata of these sensory neurons are located in the DRG.

The Posterior Column-Medial Lemniscal Pathway

The white matter dorsal funiculus is mostly composed of the central processes of DRGs. Information about the exact location and quality of tactile sensation and information from muscle, tendon, and joint receptors are combined here. As more fibers are added in a caudorostral orientation, the pathway actually grows from sacral to cervical segments, with incoming fibers always being added to the most medial section. At high cervical levels, this organization of the already placed axons from T6 and lower is visible as a "strip," the gracile funiculus (Figs. 2.5 and 2.6). The lateral group of axons, which was added above T6, is the cuneate fasciculus (Figs. 2.5 and 2.6). According to their relative position, the two tracts contain either mostly information from the upper extremities (cuneatus, begins in upper thoracic cord) or predominantly from the lower extremities (gracilis). None of these fibers decussate or have synapses in the spinal cord. Both terminate in their respective nuclei (cuneate and gracile nuclei) in the medulla oblongata. From there, the information is passed upstream via the medial lemniscus to be crossed on its way to the ventral posterior lateral nucleus of the thalamus (VPL).

The Anterolateral Pathways

Small-diameter Aδ-fibers and unmyelinated C-fibers, which transmit nociceptive and thermoreceptive information, enter the spinal cord also at the dorsal horns but then immediate synapse onto second-order neurons in the gray matter, mainly in

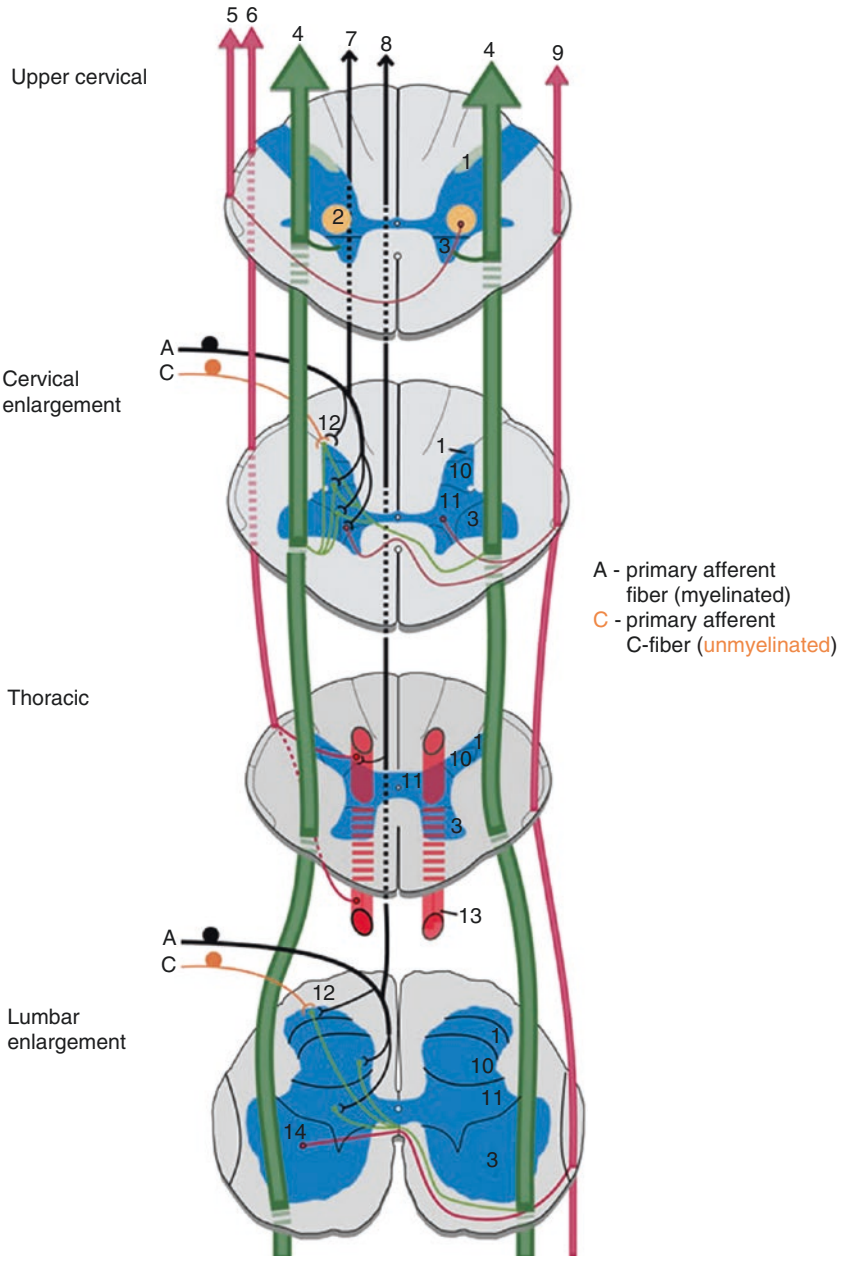

Fig. 2.6 Origin and position of ascending fiber tracts in the spinal cord. Exemplary sections from various spinal segments are shown. Filled circles represent ganglia/postsynaptic structures, open triangles depict presynaptic structures. *1* substantia gelatinosa, *2* central cervical nucleus, *3* motor nuclei of the ventral horn, *4* anterolateral fascicle, *5* central cervical spinocerebellar tract, *6* dorsal spinocerebellar tract, *7* cuneate fasciculus, *8* gracile fasciculus, *9* ventral spinocerebellar tract, *10* nucleus proprius of the dorsal horn, *11* intermediate zone, *12* marginal cell layer, *13* Clarke's column, *14* spinal border cells (adapted with permission from [79])

laminae I and V (see Sect. 2.3.1). The fibers then decussate in the anterior (ventral) commissure to ascend in the anterolateral white matter, a process which takes 2–3 spinal segments to be completed. The anterolateral pathway (Figs. 2.5 and 2.6) is composed of three distinct tracts: (1) the spinothalamic tract conveys discriminative aspects of nociception and thermoreception (e.g., location and intensity of a peripheral stimulus) and arises mostly from lamina I. As already pointed out for the posterior column-medial lemniscal pathway, a major upstream target is the VPL of the thalamus, although the pathways terminate on different neuronal populations within the VPL. Spinothalamic projections can also target other thalamic nuclei and are thought to convey similar information as the spinoreticular tract. (2) The spinoreticular pathway is considered to be phylogenetically older and transmits other aspects of nociception (e.g., arousal and emotion). This tract is composed of C-fibers that originate from more ventral laminae in the dorsal horn (e.g., VI–VIII). (3) The spinomesencephalic tract, which arises predominantly from lamina V neurons, projects to the periaqueductal gray in the midbrain and the superior colliculus. The role of the periaqueductal gray especially for micturition is discussed in Sect. 2.4. Other smaller tracts also contribute to the anterolateral system and are summarized in Table 2.2.

The Cerebellar Input System

The spinocerebellar tracts are a major source of input for the cerebellum and ascend in four tracts: the cuneocerebellar and rostral spinocerebellar tracts (upper extremities and neck) and the dorsal and ventral spinocerebellar tracts (lower extremities). Their feedback information is composed of afferent input about limb movement (cuneocerebellar tract for the upper limb and neck, dorsal spinocerebellar tract for the lower limb) and information on spinal interneuron activity during locomotion (reflective of descending pathway activity) by the rostral spinocerebellar tract for the upper limb and the ventral spinocerebellar tract for the lower limb.

The cuneocerebellar tract is composed of proprioceptive Aα- and Aß-fibers from the upper extremities, which ascend ipsilaterally in the cuneate fasciculus, but target the external cuneate nucleus positioned just lateral to the cuneate nucleus. From there, cuneocerebellar fibers further ascend to the ipsilateral cerebellum. The anatomical equivalent to this tract in the lower extremity is the dorsal spinocerebellar tract, which has its origin in a distinct group of neurons in the nucleus dorsalis (Stilling-Clarke, Fig. 2.6 [79]). The dorsal nucleus resides as a column in the dorsomedial gray matter in the intermediate zone, extending from (C8)T1 to L2/3. Neurons in this nucleus predominantly convey information from proprioceptive Aα- and Aß-fibers. Eventually, these fibers will give rise to mossy fibers in the ipsilateral cerebellum. Information transmitted via both these tracts remains unconscious, and this allows for fast feedback about current limb movement that can then be fine-tuned by the cerebellum.

The rostral spinocerebellar tract remains elusive in humans but is most likely an upper limb equivalent of the ventral spinocerebellar tract. The latter has its origin with so-called spinal border cells that reside along the outer edge of the central gray matter and from scattered neuron populations in the intermediate zone. These axons cross over in the ventral commissure and ascend in the ventral spinocerebellar tract. Before terminating in the cerebellum, the fibers cross back to the ipsilateral side.

Other fibers that have their origin within the contralateral gray matter and cross over in the commissura alba end up in a pronounced ventral position in the anterior and lateral funiculus. These fibers include the anterolateral fasciculus and the ventral cerebellar tract, which is located more superficially.

The anterior spinocerebellar tract (Fig. 2.5) has its origin mostly in neurons at the base of the ventral horn (laminae V–VII) and ascends both ipsi- and contralaterally. Information transmitted via this tract is also proprioceptive, but in a coarser fashion than in the posterior tract, because the anterior neurons have larger receptive fields in the periphery. When these fibers reach the cerebellum, they decussate back to the ipsilateral side, with the consequence that the cerebellum actually only receives ipsilateral input. Last but not least, several smaller, ascending pathways reach the cerebellum to contribute to the cerebellar input system, namely, the spino-olivary tract, terminating in the olivary nuclear complex, and the spinovestibular tract, terminating in the vestibular nuclei.

2.3.2.2 The Main Descending Pathways

The descending motor pathways are divided into lateral and medial motor systems (see Table 2.2). The general layout of these systems is that upper motoneurons (located in the primary motor cortex and adjacent regions) project to lower motoneurons in the spinal cord and brain stem. These then convey motor system information to peripheral muscles.

The Lateral Motor System

The major descending tract of the lateral motor system is the corticospinal tract (CST; Fig. 2.5), which innervates lower motoneurons in the ventral horn. It is especially important for rapid, skilled movement at individual digits and joints. Its origins are predominantly pyramidal neurons in the motor cortex, whose axons (bundled in the CST) traverse through the brain stem. Just caudal to the pyramids, about 70–90 % of the axons cross over to the contralateral side and then descend as the lateral CST. The uncrossed axons establish the narrower anterior CST, which descends very medially, right next to the median anterior fissure. Before these axons reach their target motoneurons, they largely cross to the contralateral side. The anterior CST ends in the cervical cord.

The other lateral motor system tract, the rubrospinal tract, decussates still within the brain stem and is thought to influence muscle tone of distal extremities. Its exact location and function in humans remain elusive [9, 79]. Given that the difference between the flexor posturing in the upper extremities in decorticate states and the extensor posturing in the upper extremities in decerebrate states corresponds to brainstem lesions above or below the red nucleus respectively, it is thought that the greatest impact of rubrospinal projections is on flexor motoneurons of the upper extremities.

The Medial Motor System

The tracts of the medial motor system include the abovementioned anterior CST, the vestibulospinal tracts (for head/neck position and balance), the reticulospinal tract

(automatic posture and gait-related movements), and the tectospinal tract (presumably coordination of head and eye movement). It is important to note that the lateral and medial motor systems actually work in concert, and both have voluntary and involuntary components, which act synergistically for the majority of all human movements.

The Coeruleospinal Tract

The coeruleospinal tract is best described in rodents at this point, while relatively little is known about its precise topography and function in the human. Fibers descending from the nucleus locus coeruleus and the nucleus subcoeruleus (the coeruleospinal inhibitory pathway) travel within the lateral column and provide input to all segments of the spinal cord, terminating in the posterior and anterior horns as well as the intermediate substance. In rodents, the system has been shown to have a pivotal function in pain control and processing. It provides noradrenergic innervation of the spinal cord [92], and its activation can lead to substantial antinociception [122].

2.4 Visceral Pathways and the Regulation of Micturition

2.4.1 Visceral Efferent Pathways

Visceral organs receive input from autonomic neurons that belong to either the sympathetic (arise from T1–L2/L3) or parasympathetic (cranial nuclei and S2–S4) systems. The autonomic neurons in the spinal cord are preganglionic, while neurons in the peripheral ganglia are postganglionic. Just like somato-efferent fibers of motoneurons, preganglionic neurons leave the spinal cord via the ventral roots and are cholinergic. A peripheral ganglion can easily contain several hundred sympathetic and parasympathetic contacts, which connect to a large number of postganglionic neurons that then innervate the target organ or tissue. Somata of autonomic preganglionic neurons are located in the spinal cord intermediate zone where they cluster in two distinct nuclei, namely, the intermediolateral nucleus of the lateral horn (lamina VII, T1–L2/L3; Fig. 2.7, upper panel) and the dorsolateral intermediate gray matter (S2–S4; Fig. 2.7, lower panel). The intermediolateral nucleus connects to the intermediomedial nucleus via an intricate network of fibers and dendrites [3].

Preganglionic sympathetic fibers are myelinated and comprise the white communicating rami to connect to the sympathetic trunk (Fig. 2.7, left side), where they either ascend or descend, depending on their target. They ultimately terminate on postganglionic neurons located either in the trunk's ganglia or in the abdominal prevertebral ganglia. Postganglionic fibers are unmyelinated and eventually merge with spinal nerves via the gray communicating rami (Fig. 2.7, left side). They reach their targets by forming a perivascular plexus along blood vessels.

Preganglionic neurons of the sacral cord, as outlined above, belong to the parasympathetic system. In contrast to sympathetic neurons, they terminate on

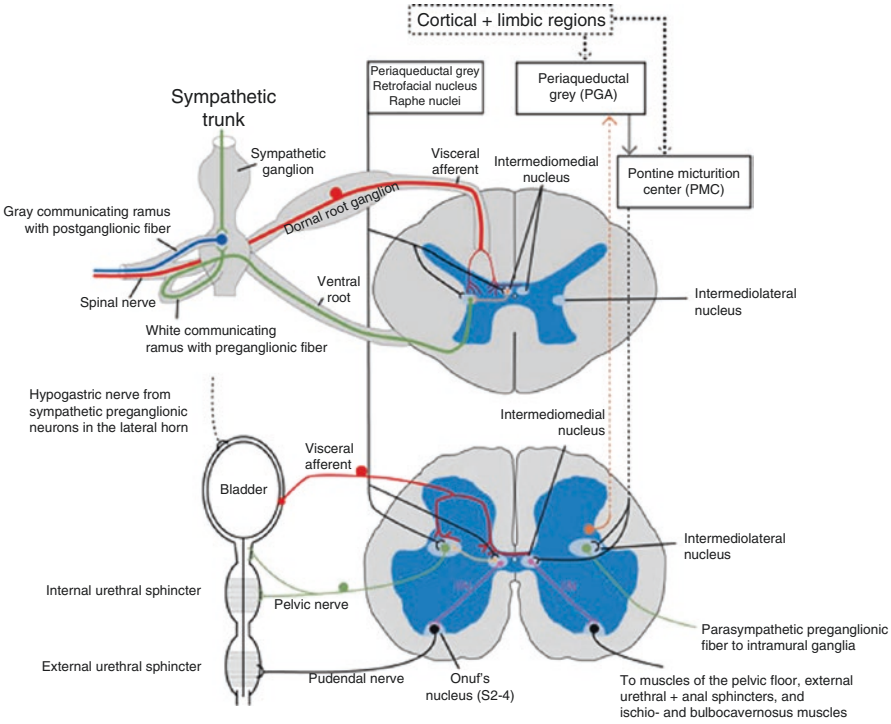

Fig. 2.7 Sympathetic and parasympathetic components of spinal micturition control. In an exemplary figure of thoracic and sacral spinal cord segments, the sympathetic trunk and bladder are depicted (*left side of image*). Thoracic myelinated fibers reach the sympathetic trunk by first joining the ventral roots and then passing through the white communicating rami. They ascend or descend to ultimately terminate on postganglionic neurons in its ganglia or those of the prevertebral plexus (not shown). Unmyelinated postganglionic fibers and pass through the gray communicating rami to join the spinal nerves. Sacral preganglionic fibers are parasympathetic and terminate on juxta- and intramural ganglia, respectively. Alternatively, they can also terminate on the autonomous plexus of the gastrointestinal tract. The periaqueductal gray (PGA), retrofacial nucleus, raphe nuclei, and hypothalamus in turn innervate the spinal autonomous nuclei (intermediolateral and intermediomedial nuclei). The PGA receives afferent information from the sacral cord and controls micturition via the pontine micturition center (PMC). The PMC innervates preganglionic neurons that regulate the contraction of the detrusor muscle of the bladder. These PMC neurons also regulate interneurons inhibiting the motoneurons of Onuf's nucleus, which innervate the external urethral sphincter. The retroambiguus nucleus, which receives direct input from the PGA and also projects to Onuf's nucleus, has been omitted in this image. (adapted with permission from [79])

intramural, or juxtamural, ganglia positioned close to their respective target organs or tissues, including the plexus of the enteric nervous system.

The spinal autonomous nuclei are innervated by several CNS structures, such as the periaqueductal gray (see Sect. 2.4.2.3), the raphe nuclei (e.g., modulation/inhibition of nociception), and, importantly, the hypothalamus (e.g., coordination of the autonomous system, endocrine regulation).

Table 2.3 Spinal control of the lower urinary tract

Class	Organ(s)	Nucleus	Nerve roots	Effect, function
Sympathetic	Bladder: neck, urethra, dome	Intermediolateral nucleus	T11–L1, hypogastric nerve	Excitatory: contraction of bladder neck Inhibitory: relaxation of dome, contraction of urethra ⇒ *Continence*
	Internal urethral sphincter			Excitatory
Parasympathetic	Bladder: detrusor muscle	Sacral parasympathetic nucleus	S2–S4, pelvic nerve	Excitatory: constriction of bladder, relaxation of urethra ⇒ *Voiding*
	Internal urethral sphincter			Inhibitory
Somatic	External urethral sphincter	Onuf's nucleus	S1–S3, pudendal nerve	Excitatory: contraction of striate muscle
	Pelvic floor	Anterior horn	S2–S4	Excitatory: rhythmic contractions
				⇒ *Continence*

modified from [9, 46]

2.4.2 Spinal Regulation of Micturition

The control of micturition is an essential physiological process for mammalian life (detoxification, territorial demarcation, estrus signaling, etc.). In adult humans, the conscious control of micturition signals is a socially very important ability. Its partial or complete loss after spinal cord injury continues to be one of the most stressful consequences of the injury (see chapter 15). Interestingly, while voiding of the bladder is controlled by a spinal reflex, humans do have at least partial voluntary control over some parts of the micturition process (control of the external sphincter muscle), which highlights the fact that a number of cerebral regions impact the complex regulation of this basic physiological event with its major regulatory center situated in the sacral spinal cord.

Three major pathways are involved in the control of the lower urinary tract: (1) sympathetic preganglionic neurons (L1–L2 mostly; responsible for continence), (2) parasympathetic preganglionic neurons (L5/L6–S1; active during voiding), and (3) somatic motoneurons (S1–S3, Onuf's nucleus; innervate the striate musculature of

the external urethral sphincter during continence). The major connections of the micturition pathways are displayed in Fig. 2.7, and the spinal control of micturition is summarized in Table 2.3.

2.4.2.1 Afferent Pathways from Bladder to Spinal Cord

Timing of micturition depends on proper signaling from the urinary tract to the CNS, not only when the bladder is filled acutely but also at all other times. Mechanosensory endings in the wall of the human bladder have been described as chains of unmyelinated varicosities in the suburothelial plexus as well as in the lamina propria, where these varicosities make contact with a specific cell type, the myofibroblasts. Combined with closely associated axon terminals, myofibroblasts have been suggested to function as stretch sensors [125, 126]. The current model is that these low threshold mechanoreceptors, which relay normal filling information from the bladder to the spinal cord, connect to myelinated Aδ-fibers. C-fibers mostly convey polymodal nociceptive information to the sacral spinal cord (reviewed in [49]).

The urethra is also innervated by afferent fibers, which are activated during urine flow, presumably by triggering mild stretch sensors [51], and remain silent during normal bladder filling.

The sacral spinal cord is the most important center for the control of micturition and not only receives sensory input from the urinary tract that it relays to central regions, but it also contains the motoneurons that directly control effector muscles of the urinary tract (detrusor muscle). Nociceptive C-fibers terminate in laminae I, II, and V–VIII. From here, their information is projected to the various areas in the brain stem (e.g., the dorsomedial, lateral, and ventrolateral parts if the periaqueductal gray (PAG)). Other brain regions that receive nociceptive bladder information include the medial hypothalamus, medial preoptic area, and the thalamus. Aδ-fibers that relay bladder filling information do not innervate the same laminae as C-fibers but rather terminate in a distinct group of neurons known as Gert's nucleus [44], located lateral of the dorsal horn, receiving input not only from the aforementioned Aδ-fibers but also from higher-order pontine micturition centers (see Sect. 2.4.2.3). Incidentally, Gert's nucleus also contains axon collaterals and dendrites of parasympathetic preganglionic motoneurons that innervate the smooth detrusor muscle.

2.4.2.2 Motor Innervation of the Bladder and Its Internal and External Sphincter Muscles

Autonomic Innervation

The detrusor muscle, a three-dimensional network of smooth muscle cells that supplies the bladder wall, is innervated by parasympathetic preganglionic motoneurons located in the sacral parasympathetic nucleus (SPN). In addition, the bladder is innervated by sympathetic autonomic motoneurons located in the upper lumbar spinal cord. They reach the bladder via the hypogastric nerve (Fig. 2.7). Generally, sympathetic innervation of the bladder is believed to contribute to a decrease in bladder pressure during the filling phase so that, overall, the number of micturition events decreases [74].

Somatomotor Innervation
The external sphincter of the bladder, which is composed of striate muscle, is innervated by motoneurons from the ventromedial Onuf's nucleus, ON [83] (Fig. 2.7). ON motoneurons act together, hence organizing the rhythmic contraction of the pelvic floor musculature to constrict not only the external sphincter of the bladder but also the anal sphincter. Interestingly, ON neurons are both somatic motoneurons in the classical sense with innervation of striate musculature under voluntary control and motoneurons that exhibit distinct autonomous function.

2.4.2.3 The Periaqueductal Gray and Pontine Micturition Center

As outlined in Sect. 2.4.2.1, two different fiber populations reach the sacral cord from the bladder, and their information is relayed to the brain stem and cortical regions. Neurons of Gert's nucleus project specifically to the central part of the PAG, while nociceptive and mechanoreceptive afferents from laminae I, II, and V target the dorsomedial, lateral, and ventrolateral PAG. The latter also reach the thalamus.

The PAG is phylogenetically very old and plays a pivotal role in basic mammalian survival by establishing projections to innervate the lower brain stem. Here, the PAG controls such vital functions as control of respiration, circulation, nociception, and locomotion, among others. In the context of micturition, the PAG governs the timing of the process. While the PAG has no direct control of the sacral motoneurons, it is the direct upstream regulator of the paramedian pontine micturition center (PMC, also known as Barrington's nucleus). The PMC is a group of neurons located in the dorsolateral pontine tegmentum [5, 46], Fig. 2.7. Experiments in cats and rats highlighted its predominant role for micturition. When stimulated, the bladder was voided [81], when lesioned, pressure-induced reflective voiding was severely impaired [5, 123]. Recent work suggests an integrative role for the PMC in coordinating the micturition reflex with forebrain activity, namely, because PMC neurons project to both spinal autonomic motoneurons innervating the pelvis and cortical neurons involved in modulating behavior, thus linking these two systems [116]. The PMC's role in humans is highlighted by the negative effects in patients suffering from spinal cord injury. Of note, upper motoneuron impairment affects descending micturition pathways, leading to severe lower urinary tract dysfunctions (reviewed in [46]). In contrast, lower motoneuron impairment after spinal cord injury (e.g., at the conus medullaris below the sacral level) negatively impacts motoneurons and sacral parasympathetic preganglionic neurons that innervate the external urethral sphincter and bladder.

Besides the PAG, there is evidence that various other cortical or forebrain regions have afferent control over the PMC and micturition control [43, 120] Fig. 2.7, such as limbic structures (preoptic area of the hypothalamus, central nucleus of the amygdala, the lateral bed nucleus of the stria terminalis) and cortical areas (anterior cingulate cortex, insula). Their specific roles remain to be elucidated, but recently, a comprehensive body of evidence has been provided pointing to tight interactions of centers controlling anxiety, sexual behavior, and sleep with micturition control centers such as the PAG and PMC to suppress voiding and strengthen continence in situations of heightened stress and allowing for the conscious decision, when and where to micturate [44, 71].

2.5 The Propriospinal System and Central Pattern Generators

Per definition, propriospinal neurons (PNs) are those that reside within the confines of the spinal cord, as compared to supraspinal neurons, which are located above the cord with axons projecting to spinal regions. The majority of PNs are interneurons connecting multiple segments and playing a fundamental role in the computation of motor reflexes and sensory input. Some of their most central roles include the coordination of information flow from and to central pattern generators (CPGs) and the modulation of these forelimb and hind limb circuits to orchestrate directed movement. As outlined in Sect. 2.5.3, CPGs are networks which generate the rhythm and pattern shape of motoneuron bursts under the control of supraspinal centers and hence function as initiators and mediators of locomotion (reviewed in [29]).

PN function is especially important in the spinal enlargements in the cervical and lumbar segments. For example, in the cervical enlargement, PNs with short axons (premotoneurons) modulate and integrate corticospinal as well as sensory information to motoneurons of upper/forelimbs, thus providing the anatomical substrate for reaching and grasping as well as more delicate hand tasks [89]. Likewise, in the lumbar enlargement, PNs control lower-/hind limb motoneurons [36]. They contribute to local spinal CPGs that control and coordinate flexor and extensor motoneurons of the shoulder/forelimb and pelvis/hind limb regions and are further connected to couple appropriate interlimb coordination to allow for rostrocaudal processing of movement initiation [48]. The latter is mediated by long-axon propriospinal projections [120]. Finally, the ventral horn gray matter is surrounded by a band of propriospinal fibers termed ground bundles (Fig. 2.4). They only descend and ascend over a few segments and play a role for fast reflex reactions.

Functional aspects other than locomotion that are modulated and coordinated by PNs include respiration and autonomic functions. Other autonomic functions are governed by groups of PNs residing in laminae II–IV of the dorsal horn and X surrounding the central canal. They are organized in ipsi- and contralateral projection circuits [62, 86] and compute nociceptive and viscero receptive input to and from the spinal cord.

2.5.1 Propriospinal Projections

Generally, two PN projections are distinguished: local short-axon projections that span only a few spinal cord segments and long-axon projections which mainly serve to connect the cervical and lumbar enlargements.

Short-axon PNs typically have their somata in the gray matter, especially lamina VII, and extend their axons intra- and intersegmentally before contacting lamina IX motoneurons or other interneurons. Humans, unlike many other mammals, have a large number of direct monosynaptic corticomotoneuronal connections, which are essential for dexterous locomotion since they have a preferential impact upon motoneurons controlling distal muscles of the upper limb. Monosynaptic connections are also of critical importance for movements that require the most voluntary control (e.g., fractionated finger movement) and are a typical hallmark of human evolution. However, many

"simpler" motor tasks, e.g., reaching and grasping, are most likely the result of CST neurons first contacting cervical short-axon premotoneurons, hence impacting motoneurons only indirectly [77]. This system is also referred to as the C3-C4 propriospinal system in humans [90]. At thoracic levels, short-axon PNs are located throughout the gray matter with the exception of lamina IX. These axons ascend or descend just a few segments and then form synapses in laminae III–VIII as well as with lamina X interneurons and lamina IX motoneurons, respectively [120]. Functionally, they control the activity of axial musculature involved in postural stability.

A similar system has been suggested in the lumbar spinal cord. Early data from the cat indicated that short-axon lumbosacral PNs are dispersed throughout the intermediate gray matter [98]. Accordingly, projections to motoneurons for the pelvic girdle and thigh musculature reside in laminae VII and VIII and receive input from the reticulospinal and vestibulospinal tracts that descend in the ventral spinal cord. On the other hand, short-axon projections to motoneurons for the distal hind limb musculature are located in laminae V–VII and, in some mammals, receive input from the rubrospinal and corticospinal tracts in the dorsal, dorsolateral, and lateral spinal cord [98]. This way, short-axon lumbosacral PNs can modulate descending brain stem information with the lumbar CPG for hind limb locomotion (reviewed in [47]; see Sect. 2.5.2).

Long-axon PN origins and projections are anatomically well described in nonhuman mammals and have their somata predominantly in lamina VIII and the medial lamina VII but can also be observed in laminae I, IV–VI, and X. Like short-axon projections, they can project bidirectionally, both rostrally and caudally, and terminate preferentially in laminae V–VIII. With less frequency, they are also observed terminating in lamina IX [4, 73] (reviewed in [33]). Moreover, they also show a high degree of both contra- and ipsilateral projections. In humans, the existence of these long-axon projections is predominantly based on evidence obtained from patients suffering from cervical spinal cord lesions. Several groups showed that after electrical stimulation of lower limb muscles, interlimb reflexes could be triggered in contralateral upper limb regions [14, 65]. Furthermore, several authors have suggested that forelimb-hind limb coordination as it is required for swimming, walking, or crawling is mediated by similar circuits coupled by long-axon PN projections [22, 119].

2.5.2 Quadruped and Biped Locomotor Propriospinal Systems

As pointed out in Sect. 2.5.1, humans have the highest number of monosynaptic descending projections with most important direct cortical-motoneuronal influence of all mammals and use especially the forelimb for both skilled hand movements and coarser movement (grasping, reaching) at the same time. It has been speculated that the gradual weakening of the propriospinal neuronal system (from e.g., cat to primate) is accompanied by a progressive strengthening of direct cortical-motoneuron projections (strongest in human), leading to the ability for skilled motor tasks with the forelimb [22, 75]. Yet at the same time, interlimb coordination in humans seems to work surprisingly similar to other quadrupedal mammals like cats [22]. Typically, quadruped locomotion requires precise spatiotemporal coordination of fore- and hind limb movement, and this is mainly accomplished by CPGs in the rostral spinal

cord (forelimb) and in the caudal spinal cord (hind limb) as well as long-axon PN projections between the cervical and lumbar enlargements and propriospinal feedback control to adapt to the environment, e.g., ground asymmetries [29, 68, 128].

2.5.2.1 Interlimb Coordination

Human bipedal gait depends on the intricate ispi- and bilateral coordination of extensors and flexors in both legs. This coordination is under the partial influence of reticulospinal projections from the reticular formation [10] (reviewed in [22]). Furthermore, lower limbs react in a coordinated manner under physiological conditions as shown, e.g., by experiments with subjects walking on split-belt treadmills where each side runs at a different speed [30]. Here, the limbs affect each other in terms of their spatiotemporal behavior. These data suggest that the spinal cord contains networks that control individual limbs and that these networks are interconnected.

In humans, a task-dependent neuronal coupling of cervical and thoracolumbar PN networks coordinating arm and leg movements has been proposed [25] (Fig. 2.8).

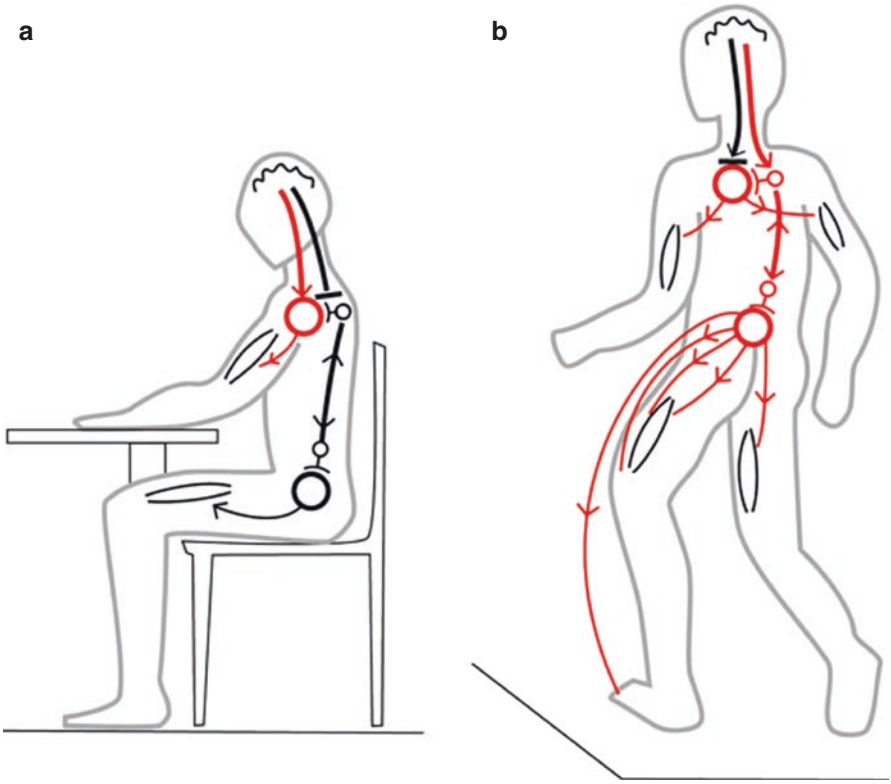

Fig. 2.8 Task-dependent movement control during different motor tasks. (**a**) A strong direct corticomotoneuronal excitation is predominant during skilled hand movements (*red lines*). At the same time, the cervical propriospinal system is inhibited (*black lines*). (**b**) During locomotion, the brain input is predominantly mediated by interneurons. Cervical and thoracolumbar propriospinal systems become coupled and coordinate arm and leg movements (*red lines*) (reprinted with permission from [24])

Supporting evidence was obtained in studies where reflex responses to tibial nerve stimulation were identified in proximal arm muscles during walking, but not during sitting or standing. Also, arm responses to tibial stimuli were not observed in subjects standing with voluntary arm swinging or subjects sitting and writing [25]. In fact, the author implies that arm swinging (associated with walking) may actually be a residual function of phylogenetically older, quadrupedal movement. This model of task-dependent activation also requires a gating mechanism that can differentiate between skilled forelimb movement (grasping, reaching) and coarser locomotion, and this function is most likely accomplished by PNs.

Another significant component of human locomotion seems to be anticipatory spinal activity. Michel and colleagues showed that proximal arm muscles are involved in the acquisition and performance of a precision locomotor task when human subjects were asked to walk on a treadmill, freely moving their arms and tasked with stepping over an obstacle [67]. Presumably, this is accomplished by an anticipatory upregulation of PN circuit activity coupling between the cervical and thoracic segments. Functionally, this resulted in a more pronounced swing of the arm over the obstacle than when walking normally. The authors concluded that the spinal reflex activity actually anticipated the subsequent arm muscle activation and is an essential component of balancing the body. If less balance is required (e.g., after body stabilization), or if subjects were verbally instructed to not expect an obstacle despite being presented with one, this upregulation of reflexes was not observed [66].

2.5.3 Central Pattern Generators

The concept of PN networks controlling distinct movement at different segmental levels is not new. In fact, intricate PN networks have been proposed over a century ago [12]. With the advances in rodent genetics and computer modeling, new insights into CPG organization have been presented in the past decades (reviewed in [38, 99]). CPGs are composed of both excitatory and inhibitory neurons (Fig. 2.9), which interact to generate rhythm and patterns for control of muscles and are under the influence of supraspinal input. Their exact cellular composition in humans remains elusive. The current models describe CPG-initiated stepping movement as follows: after gait initiation, movement-related information (e.g., position of limbs) is conveyed to spinal and supraspinal regions. Some of this afferent feedback directly modulates CPGs to assist the phase transition during the step cycle. Thus, potential environmental requirements are included in the subsequent CPG-driven computation. However, afferent feedback is also affecting motoneurons directly by modulating various reflex pathways. Those in turn are under the control of CPGs as well. The concept of this phase-dependent modulation ensures that reflex activation of a specific set of muscles only occurs at the appropriate time in the step cycle [28].

The work on human CPGs stems mostly from studies on patients with spinal cord injuries of different severity that exhibited involuntary stepping movements or

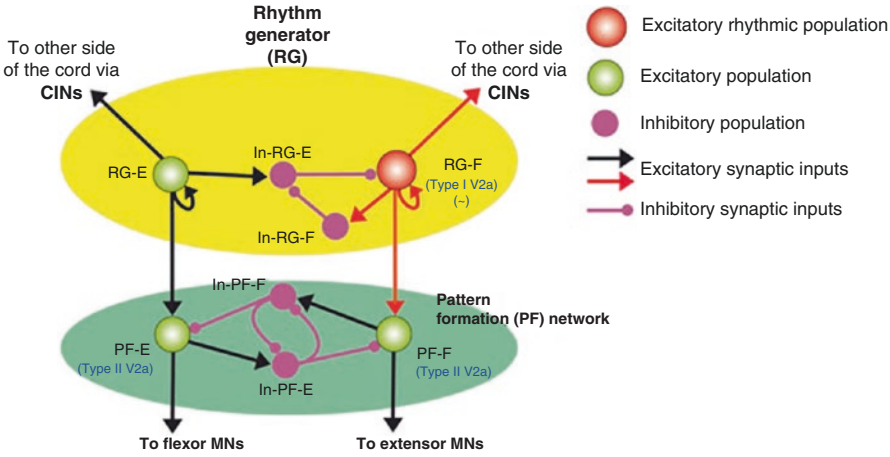

Fig. 2.9 A model of central pattern generator composition in mammalians. Schematic diagram of a two-level asymmetrical model of the locomotor CPG in mouse. This CPG controls rhythmic activity in one hemicord and consists of a rhythm generator (*RG*) and a pattern formation network (*PF*). The asymmetrical CPG has two half-centers: a flexor half-center (*RG-F* population, *red sphere*), which is intrinsically rhythmic and generates a flexor-related rhythmic activity, and a flexor half-center (*green sphere*) that is tonically active. Both interact via inhibitory interneuron populations (In-RG-E and In-RG-F). The PF contains interneuron populations (*PF-F* and *PF-E*, *green spheres*) receiving input from the corresponding RG populations. These interneuron populations also inhibit each other via inhibitory populations (In-PF-E and In-PF-F). *F* stands for flexor, *E* for extensor. See text for details (reprinted with permission from [132])

lower limb alternation, the latter only in supine position and after strong cutaneous trigger [15, 26]. Interestingly, even involuntary rhythmic muscle contractions were observed in patients with completely transected cervical or thoracic spinal cords after strong lumbar cord stimulation ([69], reviewed in [29]). Most recently, Danner and colleagues presented compelling data that suggest that the human lumbar spinal cord can form burst-generating circuits, which combine to control a wide range of movements just after receiving a simple, constant, and repetitive afferent stimulus [20] (see chapter 24). Taken together with the data obtained from laboratory animals and computational models, these studies support the idea of interneuronal networks at different segments of the spinal cord that integrate peripheral stimuli with the local reflex circuitry to provoke movement. Accordingly, in spinal cord injury, the absence of peripheral input potentially leads to the degeneration of these circuits below the level of the actual lesion or might lead to a pathophysiological dominance of inhibitory signaling to the CPG. In turn, specific training or the induction of afferent input to spinal neurons within pattern generators might offer new approaches for the prevention or at least alleviation of neuronal dysfunction in spinal cord injury [23, 32]. Apart from the classic locomotion CPG, evidence has been presented for several other types of pattern generators for other functions such as ejaculation, micturition, and scratching (reviewed in [39]).

Considering the possibly high degree of phylogenetic conservation of CPGs [85], it seems plausible to assume a conserved cellular composition of CPGs

between the species. At this point the generally accepted model for CPGs for locomotion in mammals is composed of several smaller circuits: (1) a separate CPG for each limb, (2) neural pathways within the spinal cord that coordinate these limb-specific CPGs, (3) supraspinal and afferent input, and (4) inhibitory and excitatory commissural interneurons (CINs) crossing the midline, which provide contralateral control (Fig. 2.9) [52, 63]. Under physiological conditions, contralateral inhibitory signals do not override ipsilateral signals to the corresponding motoneurons so that balanced gait is possible. To this end, CINs most likely also act as mediators between the left and right CPGs by coordinating phase relationships between the rhythms elicited by left and right CPGs [99], Fig. 2.9.

2.5.3.1 Cellular Composition of CPGs

A number of genetic studies have shed light on the identity of cells comprising CPGs in mammals (reviewed in [99]). Briefly, the following groups outlined in Sect. 2.2.4, Fig. 2.3, seem to play a fundamental role for CPG function:

1. V0 neurons, which settle in the ventral cord, generate a subgroup of neurons based on the differential expression of transcription factors including $V0_D$ neurons (dorsally located), glutamatergic $V0_V$ neurons (ventrally located), and cholinergic $V0_C$ neurons. $V0_D$ and $V0_V$ neurons project contralaterally and are involved in bilateral coordination of muscle activity [88, 111].
2. V1 neurons are a heterogeneous group of interneurons that project ipsilaterally. This group includes reciprocal Ia interneurons as well as recurrent Renshaw cells. Zhang and colleagues suggested that these neurons play a role for speed of locomotion [130].
3. V2 neurons are uniformly ipsilateral in their projection and include a group of excitatory V2a neurons and inhibitory V2b neurons [57]. Together with V1 neurons, V2b neurons play a role for maintaining alternating flexor-extensor activation. V2a neurons in turn are suggested to deliver excitatory input to $V0_V$ commissural pathways [52].
4. Excitatory V3 neurons are mainly commissural in their projections. They contribute to the maintenance of a symmetrical rhythm for locomotion [131].

How do these cells act in concert and influence flexor and extensor muscles bilaterally for locomotion? Several models have been proposed for this, and one that combines several previous models is the so-called two-level asymmetrical model of the locomotor CPG generating and controlling rhythmic activity in one hemicord [132]. A simplified version is outlined in Fig. 2.9 (from [132]). This model is based on data obtained from mouse and cat spinal cord experiments, incorporating findings from several groups. Two concepts are brought together here: a two-level CPG organization [63, 100] and an asymmetric rhythm generator with a dominant flexor half-center or a pure flexor-related rhythm generator [27]. Half-centers are defined as oscillators composed of two neurons that individually are unable to generate rhythm but produce rhythmic responses when coupled reciprocally. The function of

these half-centers can have different shapes. Depending on the synaptic release, these neurons can, for example, fire in a relative phase, even synchrony, or in fact be completely antiphasic. Another mode that has been proposed for half-centers is the "escape" and "release" mode, meaning the way the "off"-neuron turns on, either by escaping or releasing inhibition. In addition, intrinsic and network properties can also alter the function of half-centers. They therefore constitute an important component of CPGs [45].

The above mentioned model published by Zhong and colleagues has two functional levels, the rhythm generator (RG) and pattern formation networks (PF, Fig. 2.9). The RG has one intrinsically rhythmic half-center and generates flexor-related rhythmic activity (RG-F population in Fig. 2.9). Bursting activity in this cell population is based on persistent, slowly inactivating sodium currents in individual neurons and excitatory synapses between these cells in the RG-F population. On the other hand, the nonrhythmic extensor half-center (RG-E population in Fig. 2.9) is tonically active and contributes to the control of the duration of the extensor phase. Also, it controls the timing of the switch to the next flexion through the inhibitory component of the In-RG-E population. In turn, this population's activity is regulated by the rhythmic RG-F half-center via the inhibitory In-RG-F population. So in summary, the RG network, according to this model, functions as a clock and defines the locomotor frequency, drives the activity of the PF network (lower panel in Fig. 2.9), and also coordinates left and right rhythmic patterns. The latter is accomplished via CINs.

The PF network on the other hand consists of two main cell populations: PF-F (flexor) and PF-E (extensor), which initiate locomotor activity in motoneurons responsible for flexor and extensor activation, respectively. The PF-F and PF-E populations reciprocally inhibit each other via their respective interneuron pools In-PF-F- and In-PF-E (Fig. 2.9). Moreover, they coordinate the alternating activity in the flexor- and extensor-related populations of the ipsilateral locomotor network. For example, the PF-F population receives rhythmic input from the RG-F RG and in turn produces rhythmic activity for the flexor motoneurons. The PF-E population, however, obtains tonic activity from the RG-E population and is therefore rhythmically inhibited during the flexor phase during a step cycle. This is coordinated by PF-F neurons via the In-PF-F population. In turn, the PF-E population rhythmically activates extensor motoneurons and contributes to PF-F activity regulation via the inhibitory In-PF-E interneurons. This "simple" network of course is bilateral, meaning that the left and right sides of the spinal cord need to be reflected in CPG models. The model depicted in Fig. 2.9 is therefore only an ipsilateral model, omitting the CINs that connect the two sides (for a full model with bilateral organization of CPGs, refer to [132]).

Much of the concepts of CPG organization rely on animal and computational studies, and there is certainly a good chance that subpopulations of neurons with additional significant contribution are not yet known. However, the models outlined above provide a valuable basis for further studies on functional implications of CPGs and their alterations in spinal cord injury, including potential therapeutic interventions.

Conclusion

The spinal cord is a highly complex, yet rather plausibly composed anatomical region that serves as the body's major relay station for the computation of peripheral and central information. It serves not only as a major locomotion initiator but also maintains the body's ability to react fast to potentially dangerous external stimuli by providing the anatomical substrate for reflex reactions. To date, much information about spinal cord anatomy has been derived from various mammalian animal models, and a surprisingly large amount of this data has been verified in humans as well, suggesting that the complex functional network structure of the spinal cord drove (or is the consequence of) mammalian evolution. Our knowledge from different species, especially with regard to the development of locomotion patterns and interlimb movement coordination, may be in parts transferrable to human anatomy and physiology. Likewise, further development of experimental approaches with human spinal cord injury in mind offers a unique opportunity to address spinal dysfunction in patients.

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Pattern of Neurological Dysfunction in Spinal Cord Disease

3

Norbert Weidner

Abstract

Spinal cord injury includes all diseases, which affect neural structures within the spinal canal surrounded by the vertebral column, namely, the spinal cord and nerve roots leaving and entering the spinal cord. Within the spinal cord, white and gray matter contain neural structures, which represent components of both the central and peripheral nervous system. The white matter contains all long descending and ascending axon pathways mediating sensory, motor, and autonomic functions between the brain and respective end organs. The gray matter with millions of interneurons and motoneurons represents the neuronal relay station at each segmental level, which modulate sensory, motor, and autonomic function between the input and output centers. Based on the neuroanatomical organization of the neural structures within the spinal canal (spinal cord with its respective "compartments" and nerve roots), a variety of distinct patterns of neurological dysfunction relevant for clinicians, therapists, as well as scientists aiming for spinal cord repair will be described. Patterns distinguishing a spinal cord lesion from brain or peripheral nervous system disease, specific for individual spinal cord segments, as well as phenomena such as sacral sparing will be described. The relevance of the identification and description of distinct patterns in respect to the prediction of etiology, outcome, and treatment efficacy will be discussed.

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3.1 Introduction

Any kind of spinal cord disease – traumatic or nontraumatic – presents with a distinct pattern of neurological dysfunction. The relevant parameters determining this neurological pattern are as follows:

- Spatial and temporal progression of symptom presentation
- Location, quality, and severity of sensory dysfunction
- Location and severity of motor dysfunction (paresis, plegia)
- Spastic versus flaccid paresis
- Quality and severity of bladder/bowel/cardiovascular dysfunction

Why is it important to determine these parameters and the resulting pattern of neurological dysfunction? First of all, as in any other neurological disease condition, the exact neuroanatomical region relevant for the observed neurological dysfunction needs to be defined (where is the lesion?). This information is crucial in considering spinal cord damage in the first place and in directing further diagnostic workup most efficiently. For example, the radiologist needs to be directed, where along the spine to perform a CT or MRI. Ideally, the identification of defined malfunctioning neuroanatomical regions may allow one to identify the cause of spinal cord disease. For example, subacutely progressing symptoms reflecting proprioceptive dysfunction without significant motor or autonomous nervous system dysfunction are frequently found in metabolic causes of spinal cord disease such as subacute combined degeneration or copper deficiency (see chapter 8). An elderly patient presenting with a central cord syndrome following a fall at home most likely suffered a cervical spinal cord contusion with preexisting cervical stenosis.

Just determining the lesion level is important for deciding the immediate monitoring intensity required. A tetraparetic patient level C4 has a much higher risk for life-threatening complications such as respiratory distress and cardiovascular problems and therefore needs to be transferred to an intensive care unit until the cardiopulmonary condition is considered stable.

Whether a patient suffers from upper motoneuron-type versus lower motoneuron-type neurogenic bowel dysfunction determines differential treatment options. In the case of upper motoneuron-type neurogenic bowel dysfunction, reflex-based defecation is the treatment of choice; in lower motoneuron-type dysfunction, digital stool evacuation will be employed.

The pattern of neurological dysfunction allows us to predict the outcome. Patients with sacral sparing, meaning preservation of sensory and motor function in the sacral region, are classified as incomplete spinal cord injury according to the American Spinal Injury Association (ASIA) impairment scale (AIS) classification. This means they have a much higher likelihood of recovering more profoundly over time with consecutive restoration of sensorimotor and autonomous function.

The pattern of neurological dysfunction may allow us to identify patients at risk for developing complications/sequels of spinal cord injury. For example, the pattern of sensory function changes may indicate the risk of developing central neuropathic pain. Patients with a relative sparing of tactile sensation on one hand and reduced/

abolished temperature and pain sensitivity on the other hand have been described to be patients at risk to develop central neuropathic pain [1]. At this point, preventive measures do not yet exist to ameliorate or prevent the occurrence of neuropathic pain in patients at risk; however, they may become available in the future.

Considering the availability of effective regenerative therapies in the future, the precise assessment of neurological dysfunction is highly relevant. Sensorimotor completeness decides whether a SCI patient is likely to respond to a regenerative therapy, which aims to induce structural plasticity in patients with still intact descending and ascending motor and sensory pathways. A treatment, which aims to induce long distance axon regeneration or only structural plasticity immediately caudal to the injury site, heavily depends on the integrity of caudally located lower motoneurons. Therefore, in particular in cervical spinal cord injury, the extent of lower motoneuron damage needs to be defined in order to predict the efficacy of a regenerative or neurorehabilitative therapies (see chapter 21 and 24).

3.2 Pattern of Neurological Dysfunction

3.2.1 Clinical Symptoms Indicating Spinal Cord Disease

Spinal cord disease comes in different flavors (Fig. 3.1). Example 1: In an ideal textbook world, the patient reports an acute loss of sensorimotor function in the lower extremities with the inability to empty the bladder. On clinical exam there is a flaccid paraplegia with complete loss of all sensory modalities below the level T6. Catheterization of the bladder reveals 800 ml remaining urine in the bladder. In this fictive case, all relevant criteria indicating spinal cord injury are fulfilled. The lesion

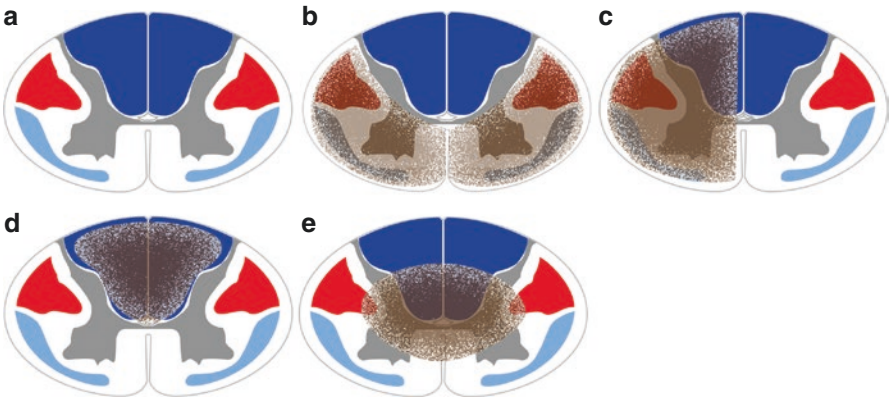

Fig. 3.1 Most common pattern of spinal cord damage in relation to the cross-sectional area affected. (**a**) Cross section of the intact spinal cord: spinal cord gray matter (*gray*), dorsal column sensory pathway (proprioceptive pathways, *dark blue*), corticospinal tract (*red*), and spinothalamic tract (*light blue*). (**b**) Anterior cord syndrome. (**c**) Brown-Sequard syndrome. (**d**) Posterior cord syndrome. (**e**) Central cord syndrome

level can be easily determined. Subsequent radiology workup will most likely confirm a midthoracic spinal cord lesion. Example 2: The opposite presentation would be a patient who is transferred with a hemiparesis of the right arm and right leg. Upon questioning he confirms that he can empty the bladder just fine. An indwelling catheter does not allow us to determine bladder function. The pattern of neurological dysfunction – hemiparesis – may suggest a cortical/subcortical lesion. Only a thorough neurological exam will allow us to detect a contralateral sensory loss for pain and temperature indicative of spinal cord damage. Thus, a careful neurological exam will prevent a false diagnosis of an acute cerebral damage such as cerebral ischemia with a potentially harmful therapeutic consequence, e.g., systemic thrombolytic treatment.

3.2.1.1 Anterior Cord Syndrome

The anterior cord syndrome involves the anterior two-thirds of the spinal cord (Fig. 3.1b). Clinically apparent, the corticospinal and the spinothalamic tract are predominantly affected with resulting paralysis and impaired sensation for temperature and pain below the lesion level. Autonomic function is frequently affected with resulting bladder, bowel, cardiovascular, and sexual dysfunction. This pattern is frequently described in the context of spinal cord ischemia resulting from anterior spinal artery occlusion, either spontaneously or in the course of thoracoabdominal vasculosurgical procedures. Furthermore, compression spinal cord injury at thoracic level resulting from median disk prolapse or fractured bone fragments can induce a similar clinical picture. Usually the prognosis in terms of recovery is less favorable.

3.2.1.2 Posterior (and Lateral) Cord Syndrome

The posterior (Fig. 3.1d) and infrequently the lateral white matter are typically affected in metabolic and toxic spinal cord disease (see chapter 8) with reduced/abolished deep sensation and consecutive sensory ataxia. Rarely a compressive cause of SCI (tumor, spinal stenosis) can be identified [2]. As soon as the lateral columns including the corticospinal tract become involved, spastic paraparesis will present. Depending on the cause, proper treatment of the metabolic cause (e.g., cobalamin substitution) can reverse symptoms and thus promote recovery of function. Isolated posterior column dysfunction due to compression spinal cord injury is rarely observed.

3.2.1.3 Unilateral Cord Syndrome (Brown-Sequard)

Unilateral cord syndrome or Brown-Sequard syndrome produces greater ipsilateral proprioceptive and motor loss, while contralaterally pain and temperature sensations are lost. Charles-Édouard Brown-Séquard was a neurologist, who described for the first time, the crossing of pain and temperature pathways at the spinal level. Brown-Sequard syndrome is caused by a hemilesion of the spinal cord (Fig. 3.1c), in most instances caused by a traumatic cause, mostly motor vehicle accidents, gunshot wounds, and assaults. Nontraumatic cases are frequently associated with compressing tumors or spinal stenosis [2]. A rare condition – idiopathic spinal cord

herniation – leads in almost all instances to a Brown-Sequard syndrome after ventral displacement of the anterior or anteriolateral funiculus unilaterally at thoracic level [3]. Although not common, spinal cord ischemia in particular at cervical levels can lead to a unilateral spinal cord syndrome [4]. Less than 20 % of all defined SCI syndromes have been described as Brown-Sequard syndrome [2].

3.2.1.4 Central Cord Syndrome

Central cord syndrome, which refers to a lesion of the central region in the cervical spinal cord (Fig. 3.1e), is characterized by a disproportionately more severe motor impairment in the upper versus the lower extremities. A difference of at least ten motor score points in the upper versus the lower extremities supports the diagnosis of a central cord syndrome according to a consensus paper [5]. It was previously thought that a somatotopic orientation of corticospinal axons within the cervical spinal cord accounted for the predominant dysfunction of upper extremity motor performance in central cord syndrome. However in primates, a somatotopic orientation of this descending pathway cannot be confirmed. Alternatively, the corticospinal tract mediates skilled arm and hand movement more so than voluntary lower extremity movement [6], and therefore central cord lesions affecting predominantly the CST induce disproportionate functional deficits in the upper extremities. Another potential explanation – lower motoneuron damage in the ventral horn of the cervical spinal cord – is being debated. Central cord syndrome is considered as the SCI syndrome of the elderly with an average age of 53 years. The most frequent etiology is traumatic injuries due to falls followed by motor vehicle accidents [2]. Central cord syndrome has a relatively good prognosis in terms of recovery of (lower extremity) function. Out of all defined incomplete SCI syndromes, central cord syndrome is the most frequent one accounting for almost 50 % of the individuals [2].

3.2.1.5 Complete Spinal Cord Injury

According to the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) published by ASIA [7], complete spinal cord injury is defined as the absence of sensory and motor function in the sacral segments S4–5. Clinically speaking it means the absence of light touch/pinprick sensation in the dermatomes S4–5 and deep anal pressure as well as the absence of voluntary anal sphincter contraction. Severe compression/contusion of the spinal cord leads to a typical pattern of spinal cord destruction. The center of the cord is completely destroyed, whereas an outer rim of white matter tracts remains intact, even in the majority cases of clinically complete spinal cord injury [8]. It has been assumed that descending motor pathways such as the corticospinal tract and ascending sensory pathways such as the spinothalamic tract and the proprioceptive pathways running in the funiculus dorsalis are organized in a somatotopic fashion. Accordingly, sacral axons are considered to be located in the most eccentric position being regularly spared in severe but not complete SCI. However, a somatotopic layering of defined axon pathways has only been confirmed for the dorsal column proprioceptive pathways [9].

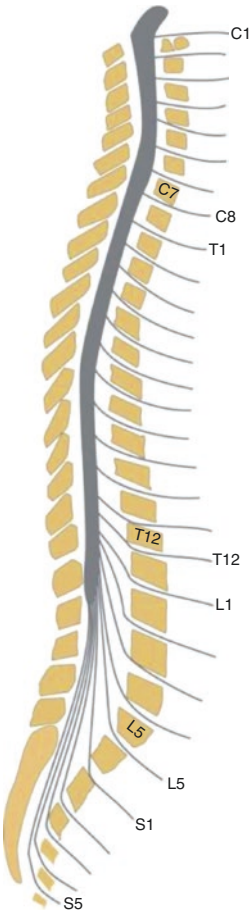

Fig. 3.2 Spatial relationship between vertebral column (cervical, thoracic, lumbar, sacral vertebrae) and related spinal cord segments

Complete spinal cord injury represents the most prevalent pattern of spinal cord disease. In a retrospective analysis of 839 patients with traumatic and nontraumatic spinal cord injury, 175 patients (20.9 %) had incomplete SCI with a defined neurological pattern (e.g., central cord syndrome, anterior cord syndrome, Brown-Sequard syndrome). The remainder were complete spinal cord injuries and incomplete spinal cord injuries, which did not fit into defined incomplete SCI syndromes as described above. In this study it was not specified how many out of these 664 patients were actually complete SCI. Precise data in this respect are only available from studies and investigation of traumatic spinal cord injury. They show that 44.5 % of patients (out of 1992 patients), which were prospectively investigated in the EMSCI (European Multicenter Study about Spinal Cord Injury, www.emsci.org) database, suffered from complete spinal cord injury (Rupp, unpublished data). For obvious reasons, they have the most unfavorable diagnosis with only around 25–30 % of the patients converting to incomplete SCI grades (see chapter 4). However, in most instances, conversion to incomplete SCI does not necessarily lead to relevant recovery of function.

3.2.2 Rostro-caudal Pattern (Lesion Level)

The clinical presentation of spinal cord disease depends – besides the cross-sectional location of the lesion – on the segmental neurological level of injury (NLI) (Fig. 3.2).

3.2.2.1 Cervical Spinal Cord

Cervical spinal cord disease is typically characterized by sensorimotor deficits in all four extremities – tetraparesis or tetraplegia – with a varying degree of autonomous nervous system dysfunction. Depending on the cross-sectional lesion extent, both upper motoneuron and lower motoneuron-type paresis can be observed in the upper extremities due to the variable impact on the corticospinal tract and/or anterior horn motoneurons.

Very high cervical lesions (at the level of the foramen magnum) can be accompanied by signs of lower cranial nerve involvement resulting in dysarthria, dysphonia, or dysphagia. In cases of C1–C4 involvement, clinical signs may be challenging since localizing symptoms may not be present. Rather non-specific signs such as pain in the neck and occipital or shoulder region may be present. At and above the C3–C5 level, upper and lower motoneuron lesions may affect motor pathways innervating the diaphragm, which can severely influence diaphragm muscle function and thus cause respiratory failure requiring artificial ventilation. Besides high cervical spine fracture, several nontraumatic etiologies such as Arnold-Chiari malformation, rheumatic arthritis, Down syndrome, syringomyelia, multiple sclerosis, and a variety of tumors including meningiomas can affect the most rostral portions of the cervical spinal cord.

Lesions between C4 and Th1 can be more precisely located based on the symptoms and neurological examination. In particular extradural lesions (e.g., tumors, herniated disks) affect initially nerve roots with respective dermatomal and myotomal dysfunction. Mixed upper and lower motoneuron signs are expressed by absent or reduced muscle stretch reflexes at the lesion level with hyperactive reflexes related to more caudal segments (e.g., in a C5/6 lesion a decreased or absent brachioradialis reflex with hyperactive finger flexor reflexes can be found). Forty-nine percent of all traumatic or ischemic SCI patients suffer from a cervical spinal cord injury according to the EMSCI database (R. Rupp, unpublished data). At 1 year after injury, the majority of cervical spinal cord injuries (SCIs) are motor incomplete (AIS (ASIA Impairment Scale)-C/-D) and account for 57 % of all SCIs in the EMSCI cohort, (R. Rupp, unpublished data; Fig. 3.3) (see chapter 22).

3.2.2.2 Thoracic Spinal Cord

SCI at thoracic levels accounts for 38 % of all traumatic and ischemic SCIs according to the EMSCI database (R. Rupp, unpublished data). The typical clinical pattern observed in complete thoracic spinal cord disease is absent sensorimotor function with concomitant bladder and bowel dysfunction. Almost two-thirds (59 %) of all traumatic and ischemic thoracic SCI patients are sensorimotor complete (AIS-A, Fig. 3.3). Depending on the level of injury, control of the sympathetic nervous system is impaired leading to autonomous dysregulation and dysreflexia causing abrupt and potentially severe blood pressure and heart rate disturbances. A careful sensory examination is

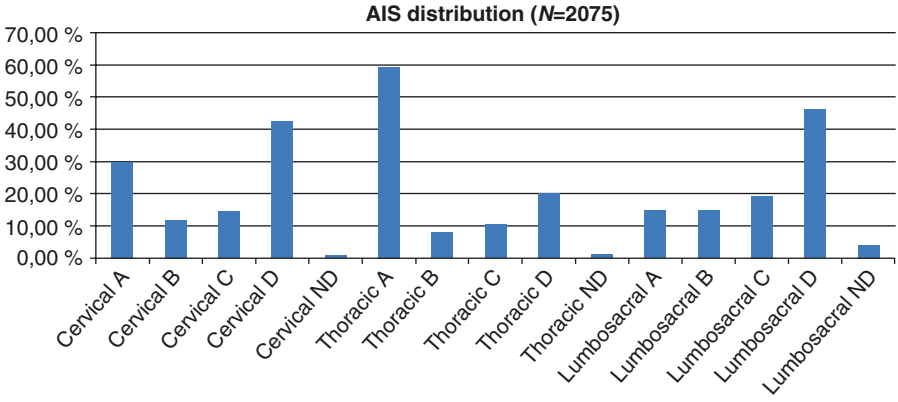

Fig. 3.3 Distribution of traumatic and ischemic SCI in respect to cervical, thoracic, and lumbosacral neurological level of injury (NLI) and injury severity (ASIA impairment scale (AIS) grades) (Data are derived from the EMSCI database (R. Rupp, unpublished data))

required to determine the level of injury. Distinct clinical motor exams, which might provide localization-related information, are not available for the thoracic spinal cord.

3.2.2.3 Conus Medullaris and Cauda Equina

Conus medullaris and cauda equina injuries are discussed together since they cannot be clearly differentiated clinically. The lumbar sympathetic, sacral parasympathetic, and lumbar/sacral somatic nerves all originate within the conus medullaris (see chapter 2). The spinal cord region immediately rostral to the conus is termed the epiconus. Unlike the cervical and the thoracic spinal cord and the respective surrounding spine, the conus medullaris is condensed to less than two vertebral heights. Typically the conus medullaris stretches from the T12/L1 disk space caudal to the middle third of the L2 vertebral body. Within this short distance, around ten segments (L1-S5) are condensed in the conus medullaris. Therefore, individual lumbar and sacral segments of the spinal cord are no longer in a close spatial relationship to their respective vertebrae (see chapter 2).

On neurological exam lesions of the epiconal region are above the T12 vertebral level and present as upper motoneuron-type SCI with a spastic paraparesis, increased tendon reflexes, and bladder-sphincter dyssynergia developing over time (Table 3.1). In respect to the NLI, NLIs above T10 tend to show upper motoneuron-type phenotypes, whereas NLIs below T12 present as flaccid paraparesis/flaccid plegia [11] with permanently absent tendon reflexes. NLIs between T10 and T12 represent a mixed zone with signs of both upper and lower motoneuron damage.

Lesion to the conus medullaris produces a neurological level of injury between T12 and S4/5 and presents with mostly symmetrical sensorimotor deficits, a flaccid muscle tone, and an atonic bladder with flaccid anal sphincter. Paraparesis can affect all lower extremity muscles and sensory function stretching all the way to the

Table 3.1 Summary of complete epiconus, conus medullaris, and cauda equina syndrome[a]

Neurological syndrome	Neurological level of injury (NLI)	Clinical examination	Neurophysiological testing	Bowel, bladder, and sexual function
Epiconus	Above T12	Conus segments intact, upper motoneuron syndrome, BCR & AR preserved, muscle tone increased	EMG, nerve conduction studies, F-wave, H-reflex intact, SSEPs: tibial and pudendal abolished	Bladder–bowel dysfunction, upper motoneuron type (bladder–detrusor-sphincter dyssynergia), sexual dysfunction (in men preserved reflexogenic erections, loss of psychogenic erection)
Conus medullaris	T12–L1 to S4–5	Complete damage of conus medullaris, lower motoneuron syndrome, all reflexes (sacral & limbs) abolished, muscle tone flaccid, muscle atrophies	Nerve conduction studies: tibial & peroneal nerves show axonal damage (<10 days); EMG, limb and sacral myotomes show severe denervation; SSEPs, tibial and pudendal abolished	Bladder–bowel dysfunction, lower motoneuron type (atonic bladder and flaccid anal sphincter), sexual dysfunction (in men loss of reflexogenic erection, psychogenic erection preserved)
Cauda equina	Below L-2	Lower motoneuron syndrome; motor, variable lower extremities weakness, diminished tone; sensory, variable sensory deficits; reflexes reduced or abolished below level of injury	Nerve conduction studies: tibial (L5–S1) and peroneal (L4–5) show axonal damage dependent on level of injury; EMG, normal proximal limb, denervation distal limb and sacral; SSEPs, pudendal affected, tibial may be preserved	Bladder–bowel dysfunction, lower motoneuron type (atonic bladder and flaccid anal sphincter), sexual dysfunction (in men loss of reflexogenic erection, psychogenic erection preserved)

Adapted from Kingwell et al. [10]
Abbreviations: *AR* adductor reflex, *BCR* bulbocavernosus, *SSEP* somatosensory evoked potential
[a]Reflects a summary of complete lesions; more variations will be observed for incomplete lesions

anal/perianal sacral dermatomes (so-called saddle anesthesia). However, a conus medullaris syndrome can be mixed with upper motoneuron signs such as brisk tendon reflexes, increased tone, and pyramidal signs. Neurophysiological exams show reduced or absent motor responses in respective nerve conduction studies (tibial and peroneal nerve), while sensory nerve conduction studies (sural nerve) are normal (supraganglionic lesion). EMG recordings typically show signs of acute denervation.

The pure cauda equina syndrome, induced by damage to the nerve roots traveling caudal to the conus all the way to their neuroforaminal exits leaving the spinal canal, has a typical NLI below L2 with more asymmetrical sensorimotor deficits affecting predominantly the L5 and S1 myotomes. There is an atonic bladder with a flaccid sphincter tone, which frequently cannot be distinguished from neurogenic bladder/bowel dysfunction in conus medullaris syndrome.

In a retrospective review analyzing 839 traumatic and nontraumatic SCIs, 1.7 % were classified as conus medullaris syndrome (mixed upper and lower motoneuron signs) and 5.2 % as cauda equina syndrome (only motoneuron signs). In the EMSCI cohort, 13 % of the patients suffered from SCI with lesion levels from L1 through S5 (R. Rupp, unpublished data) which serves as an estimate for the incidence of conus medullaris and cauda equina syndrome in traumatic and ischemic spinal cord injury. The clinical assessment did not allow to distinguish between the two syndromes nor were the patients examined in a standardized fashion for upper versus lower motoneuron signs.

3.2.3 Upper Versus Lower Motoneuron Pattern

Typically, spinal cord injury is considered a CNS disorder. Therefore, the clinical phenotype of a spinal cord-injured subject should present as an upper motoneuron injury with respective signs such as brisk tendon reflexes, spasticity, and pyramidal signs. However, in spinal cord injury there are exceptions to the rule, primarily in the cervical and in the lumbosacral spinal cord.

In the cervical spinal cord, motoneurons in the ventral horn exit the spinal cord to innervate proximal and distal arm muscles. In case of an injury to the cervical cord at a particular level, not only long descending motor pathways, such as the corticospinal tract in the dorsolateral column, are harmed. Depending on the cross-sectional location and extent of the lesion, motoneurons in the ventral horn will be directly or indirectly harmed. Postmortem studies indicate that the closer the injury is to the respective segmental level, the more likely motoneurons are damaged in the respective segmental level [12]. This is also supported by clinical studies confirming lower motoneuron damage mainly in myotomes close to or identical with the NLI by EMG, reflex activity (M-wave), and electrical stimulation (strength duration curve) in subacute to chronic SCI subjects [13]. This points toward a primarily direct effect of the injury. Our own recent investigations employing EMG, electrical stimulation, and upper extremity muscle MRI in acute cervical SCI patients over the course of 1 year instead support the notion that lower

motoneurons damage, albeit incomplete, is much more longitudinally extensive than commonly thought (S. Franz, DMGP Annual Meeting 2014). This finding is supported in the older literature on cervical SCI (Doerr & Long, Orthotics and Prosthetics 1973), where acute denervation determined by EMG can be found in flexor digitorum muscles (innervated from C8) in three out of three C4 SCI patients. Similar effects have been observed in a study, which examined lower motoneuron damage in high thoracic and cervical SCI subjects [14]. After not having identified any signs of lower motoneurons damage with EMG within the first 14 days after injury, all patients showed fibrillations and positive sharp waves at time points from 16 days up to 40 days post-injury (latest time point examined). This observation was supported by absent M-waves in peroneal nerve conduction studies and clear signs of neuropathic muscular atrophy in muscle biopsy studies. The question is still open as to whether indirect effects, such as transsynaptic degeneration or proapoptotic mechanisms activated even remotely from the actual injury site, can cause motoneuron cell death. Depending on the level of injury, patients present with clinical signs of lower motoneuron damage such as flaccid tone, decreased/absent tendon reflexes, and muscle wasting and atrophy.

Of course, in the thoracic spinal cord, motoneurons in the ventral horn can be affected just like in the cervical spinal cord following injury. However, here motoneuron damage over a few segments has little functional impact, since upper and lower extremity muscles are spared.

In contrast, in the lumbosacral spinal cord, the lower the motoneuron damage becomes more frequent, the closer the lesion comes to the conus medullaris. The diameter of the cord steadily decreases in the rostro-caudal direction. Therefore, a similar size contusion injury, compared to the cervical spinal cord, has a considerably greater impact on the nervous tissue. Besides leg muscles, external sphincteric muscles of the bladder and bowel show persistent flaccid paresis. As pointed out above, there appears to be a transition zone in lower thoracic and lumbar segments, which defines an upper versus a lower motoneuron-type injury. A retrospective analysis of complete thoracolumbar SCI cases revealed that above the NLI T10, patients show a predominant upper motoneuron-type injury, whereas below NLI T12 the majority of patients have a flaccid paraparesis. Interestingly, up to the highest NLI examined (T7) lower motoneuron-type paraparesis was observed. As a caveat, this distinction was exclusively based on neurological exam (the presence/absence of deep tendon reflexes, Babinski reflex, bulbocavernosus reflex) [11].

3.2.4 Autonomic Dysfunction in Relation to Lesion Level and Horizontal Lesion Extent

Here it is referred only to the most prominent clinically notable symptoms of autonomic dysfunction, namely, bowel and bladder dysfunction, autonomic dysreflexia, and orthostatic dysfunction. Their clinical presentation will be correlated with the lesion level and lesion extent.

3.2.4.1 Lesion Extent and Autonomic Dysfunction

As described in the context of "sacral sparing," a complete loss of sensory and motor function in the bladder and bowel sphincter region is observed in the most severe cases of spinal cord injury affecting more or less the complete circumference of the spinal cord. This does not directly translate to cauda equina lesions. Here lower sacral nerve roots can be lesioned selectively leading to an almost exclusive bowel and/or bladder sphincter paralysis with loss of sensation in this region. Sensorimotor function in the lower extremities can remain completely intact.

Supraspinal control of bladder, bowel, and cardiovascular function is mediated predominantly in the dorsolateral (raphespinal tract) and ventral funiculus (coerulospinal tract) of the spinal cord. Therefore, in anterior cord syndrome (Fig. 3.1b), autonomic function is frequently affected, whereas lesions confined to the dorsal funiculus rarely induce bladder, bowel, or cardiovascular dysfunction.

Interestingly, presentation of autonomic dysreflexia as determined by an increase of at least 20 mmHg systolic blood pressure after bladder filling stimuli does not correlate with injury completeness versus incompleteness [15]. However, there was a strong trend indicating highest rates of elevated systolic blood pressure and symptoms of autonomic dysreflexia in AIS-B patients.

3.2.4.2 Lesion Level

Neurogenic bladder dysfunction – also called "neurogenic bladder" – is the consequence of disruption of either CNS pathways or peripheral nerves controlling bladder and urethral reflexes with associated loss of bulbospinal control and coordinated interaction between the autonomic and somatic nervous system [16]. The clinical symptoms of neurogenic bladder dysfunction can help to differentiate between an upper and a lower motoneuron type underlying the para- or tetraparesis. A more precise determination of the lesion level just by neurogenic bladder dysfunction is not possible. In case of an underlying upper motoneuron lesion – any lesion rostral to the conus medullaris containing the sacral spinal cord segments and corresponding to lumbar vertebra L1/2 – coordinated contraction and relaxation of the bladder detrusor, urethra, and urethral sphincter are impaired or completely lost. As a consequence, after an initial phase of spinal shock bladder hyperreflexia, dysfunctional relaxation of the bladder neck and detrusor-sphincter dyssynergia develops [16] (see chapter 15). In these cases patients have difficulties or are unable to eliminate urine from the bladder. In contrast, lower motoneuron-type neurogenic bladder dysfunction, where the conus medullaris (lower sacral segments) and/or the cauda equina is affected, is characterized by areflexic bladder and anal external sphincter muscles. If, in addition, the L1/2 segments within the conus medullaris are affected, sympathetic innervation of the internal sphincter muscle is impaired decreasing internal smooth muscle sphincter contraction [16]. Thus, urine can neither be stored nor properly eliminated.

In neurogenic bowel dysfunction, signs and symptoms are quite similar compared to neurogenic bladder. Corresponding to the neurogenic bladder, the neurological level of injury can be divided in to upper motoneuron-type neurogenic bowel dysfunction observed in spinal cord lesions above the lower sacral segments of the

conus medullaris or in to lower motoneuron-type neurogenic bowel dysfunction based on lesions of the sacral segments within the conus medullaris or respective nerve roots in the cauda equina. Unlike neurogenic bladder dysfunction, the distinction between the two types of bowel dysfunction is more difficult. The gastrointestinal system – just like the lower urinary tract – receives neural input from the parasympathetic, sympathetic, and somatic nervous system. In addition, the enteric nervous system directly controls the smooth muscles activity in the gut. Upper motoneuron-type neurogenic bowel dysfunction shows constipation with fecal retention frequently accompanied by a spastic anal sphincter. The overall mouth-to-cecum transit time is prolonged [17], which can be attributed to abnormal segmental peristalsis and a hyperactive holding reflex with a spastic external sphincter muscle. Due to the preservation of local anal reflex circuitries, digital reflex stimulation can, in most instances, effectively elicit stool evacuation. In lower motoneuron-type neurogenic bowel dysfunction, the lower gastrointestinal tract is described as areflexic. Clinical hallmarks are slow stool propulsion in the transverse, descending, and rectosigmoid colon and constipation. The external anal sphincter muscle is frequently denervated with the risk of associated incontinence. Digital stimulation does frequently not promote reflexic stool evacuation. Overall, upper motoneuron bowel dysfunction causes broad colonic dysfunction, whereas bowel dysfunction in lower motoneuron-type SCI is confined primarily to the rectosigmoid colon [18].

In terms of cardiovascular dysfunction after SCI, supraspinal parasympathetic input is usually not altered since it is transmitted through the vagal nerve (medulla to peripheral nervous system) controlling the heart rate (bradycardia) and resting blood pressure (hypotension due to vasodilation). The extent of sympathetic alterations depends predominantly on the NLI. The more rostral to the T6 segment spinal cord injuries are located, the more severely control of sympathetic output (blood vessel constriction with increase in blood pressure) is affected – sympathetic preganglionic neurons innervating blood vessels in abdominal, pelvic, and lower body blood vessels are located in segments T5 through L1 – with consecutive orthostatic hypotension (dizziness, nausea, light-headedness), hypothermia, and bradycardia (vagal input is not counterbalanced by appropriate sympathetic input) (see chapter 14). The more rostral the neurological level of injury is, the more severe orthostatic hypotension and bradycardia are. Taken together, severe presentations of bradycardia and orthostatic hypotension indicate complete spinal cord lesion rostral to the T6 level [16]. However, over time orthostatic dysregulation and bradycardia become compensated and allow mobilization/verticalization of the patient for more prolonged periods.

In subacute and chronic SCI, orthostatic hypotension and bradycardia become less prominent, whereas autonomic dysreflexia, which is defined as an increase in blood pressure (according to the Consortium of Spinal Cord Medicine, 20–40 mmHg higher than baseline RR) with concomitant slowing of the pulse rate and related clinical symptoms in response to visceral or cutaneous stimuli (usually noxious) below the level of spinal cord lesion, can represent a chronically recurring and disabling clinical problem. Autonomic dysreflexia has been described in many textbooks to occur in neurological levels of injury T6 and above. Most commonly, triggers are derived from the lower urinary tract. More recent studies confirm this

delineation in principle. Blood pressure increases correlate inversely with the lesion level and therefore autonomic dysfunction is higher in cervical versus thoracic and lumbar NLIs. However, looking at the incidence of autonomic dysreflexia in SCI above T6 versus below, 42.6 and 15.4 % are affected, respectively [15].

3.2.5 Sacral Sparing

Sacral sparing refers to the preservation of sensation in the perianal/rectal area representing the S3 through S5 dermatomes and motor function of the rectal sphincter muscle (S3 through S5 myotomes). According to an evaluation in complete tetraplegic patients, the absence of sensory and motor function in this region represents the most severe spinal cord injury condition with few patients converting to less severe (incomplete) SCI conditions [19] (see chapter 4). Neuroanatomically this is considered to be reflected by a presumed somatotopic representation of long ascending sensory and descending motor projections with sacral axons being centrifugally located toward the surface of the spinal cord. However, there is only convincing evidence for a somatotopic organization in the dorsal column ascending pathways [9]. For all other descending and ascending pathways, in particular for the corticospinal tract [6], somatotopic organization has yet to be confirmed. Since severe SCI predominantly destroys the center of the cord diameter, a peripheral rim of axons including fibers representing the sacral dermatomes and myotomes may remain intact.

3.2.6 Conversion (Motor Paralysis) Disorder

Conversion motor paralysis disorder is considered to be common in young female individuals, although other case series describe predominant occurrence in men [20, 21]. In conversion disorder, a somatic cause cannot be identified. Typically affected patients show clinical signs and symptoms, which are not compatible with a defined neuroanatomical lesion site as described above. Depending on the case series description, mono- and paraparesis represent the most common clinical presentations of conversion disorder. However hemiplegia and tetraplegia are also observed. Typically the complete extremity is paralyzed as opposed to a central paralysis pattern (flexor muscles affected in lower and extensor muscles predominantly affected in upper extremity muscles). During a detailed motor exam, the lower extremities cannot be moved against gravity; however, the patient is able to stand and walk with barely any therapist support. Frequently, a dragging gait with external or internal hip rotation can be observed. Similarly, hip extension is determined to be weak. While testing contralateral hip flexion, hip extension, which is supposed to be weak, appears to be strong (Hoover's sign). Even though it is termed frequently as a motor or movement conversion disorder, additional signs of sensory and autonomous dysfunction are frequently observed. Patients report sensory dysfunction borders identical with anatomical borders such as the groin or shoulder; vibration sense above

the sternum or on the forehead is disturbed or hemisensory dysfunction ending exactly at the midline as opposed to the paramedian border is described.

Conclusion

Overall, careful assessment of the medical history and clinical examination will guide the clinician to initiate appropriate ancillary tests, which will help to confirm the diagnosis and identify an underlying etiology. Moreover, prognostic information can be drawn from a standardized neurological examination and additional neurological signs (e.g., muscular atrophy in cervical spinal cord injury). Early identification of the lesion level is a prerequisite to anticipate potential complications such as autonomic dysreflexia.

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Natural Course of Disease of Spinal Cord Injury

4

Martin Schubert

Abstract

The natural course of disease in spinal cord injury is well known for traumatic etiologies. In the following chapter, this will be illustrated with respect to anatomical and physiological adaptations in the central and peripheral nervous system. Disease course is described for functional recovery in the domains relevant for spinal cord injury (SCI). Underlying mechanisms of adaptation are addressed in the context of neurological and functional recovery. The role and disease course of etiologies, other than traumatic, are discussed together with the effects of treatment, where treatment is available.

In a final outlook, recovery mechanisms are discussed in the context of incipient clinical trials to cure traumatic SCI. A key issue in this context is to distinguish treatment effects from natural recovery, in order to deal with the difficulty of determining potential efficacy of an intervention. In this context, understanding of the disease course may require additional knowledge of underlying neurophysiological and pathophysiological adaptations that are not clinically evident but require technical examinations. This may help in the process of trial design and therapy development. Stratification and prediction strategies are crucial in this process.

4.1 Introduction

Spinal cord injury (SCI) has had the connotation of being an "ailment not to be treated" for more than four millennia [1]. The earliest testimony of two cases of spinal injury dates back to about 2500 years BC and is found in an ancient Egyptian

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surgical papyrus attributed to Imhotep which was found in Luxor, Egypt, in 1862 and was first translated from the hieratic and published in 1930 under the patronage of the New-York Historical Society [2]. The document includes several descriptions of what were most likely war injuries. Out of 48 cases, six affected the spine and two of them the spinal cord. The script includes commentaries and recommendations for treatment of all but these two injuries of the spinal cord, thus demonstrating therapeutic nihilism which expressed the futile prognosis of such a devastating injury. This proved true for many centuries until about 100 years ago. First systematic data were derived from the countless cases of gunshot wounds during World War I, and an early observation on the natural course of such types of traumatic spinal cord injury is expressed in a report from the 14th General Base Hospital in France by the famous American neurosurgeon Harvey Cushing, in stating that "80 % died in the first few weeks (and)… only those cases survived in which the spinal lesion was a partial one" [3, 4]. Of note, these soldiers as many others incurring spinal cord lesion did not die from the immediate injury but from subsequent complications mainly affecting their urinary tract and kidneys and in high cervical lesions at shorter intervals resulting in respiratory failure due to high lesion level, pneumonia, and cardiac arrest. Thus when describing the natural course of disease of SCI, it must be borne in mind that this could only be observed once these complications became curable following the discovery and development of antibiotic treatment [5] and following the onset of comprehensive care as employed by pioneers such as Walter Munroe (1898–1978) in the USA and Sir Ludwig Guttmann (1899–1980) in the UK. The institution of centers specialized and dedicated to the care of this patient group allowed the increase of SCI patients' life expectancy, thus making possible and necessary the development of approaches for specialized rehabilitation and lifelong care. However, even nowadays life expectancy is still reduced in SCI as compared to the general population depending on severity and the level of spinal lesion, and during the past 30 years, there was no further improvement based on recent assessments in very large cohorts [6–8]. As was noticed by Harvey Cushing in the early 1900s, incomplete SCI has a more favorable outcome which nowadays leads to a differential treatment and road map of rehabilitation in cases with complete as opposed to incomplete spinal cord injury. We have come to understand that in cases of incomplete injury, there seem to be a multitude of neural mechanisms and processes aiming at repair and reorganization [9, 10]. Understanding these mechanisms and their time course will be crucial in fostering recovery. In describing the natural course of disease and recovery, we will have to make the same distinction between complete and incomplete injury in order to acknowledge underlying differences in pathophysiology and delineate proper conclusions for the design of research approaches and therapies. Another distinction may be made with respect to pathology and the acuteness of injury. The natural history of recovery of neurological deficits and functional independence after traumatic SCI is nowadays well known from large databases which pool standardized information from hundreds to thousands of patients [11–14] and help us to understand their perspectives and prognoses. In this chapter these observations will be described with respect to groups defined by pathology, severity, lesion level, and also etiology of spinal injury.

4.2 Disease Course and Recovery Depend on Pathology

In acute traumatic spinal injuries, prognosis and recovery depend primarily on lesion severity and on lesion level [14, 15]. This is expressed in an internationally accepted gold standard of clinical assessment by segmental motor and sensory testing, according to the International Standards for Neurological Classification of SCI (ISNCSCI), which leads to the derivate of a five-step impairment scale (A–E) which was jointly produced by the International Spinal Cord Society (ISCoS) and American Spinal Injury Association (ASIA) and has been updated according to progress in the field [16, 17]. It replaced similar earlier systems, the first of which was established in Stoke Mandeville by Frankel in the late 1960s [18]. Clinical recovery can be predicted by this standardized assessment, with a particular emphasis on the state of incompleteness of the lesion, which is classified by the presence of sacral sparing [19, 20]. Individuals who are motor complete with extended zones of sensory preservation, but without sacral sparing, are less likely to convert to motor-incomplete status than those with sacral sparing of sensation (13.3 % vs. 53.6 %; $p < .001$). Motor score improvements at 1 year are related to severity of injury, with greater increases for less motor-complete lesions. Thus, neurological recovery after SCI is influenced by the severity of injury [14]. Most improvements are observed within the first year after injury with a steeper curve of recovery of strength and motor scores during the first 3 months independent of lesion level and severity [12]. However, late improvements can be seen between 1 and 5 years after SCI, while the functional significance of these changes remains unclear [21].

Traumatic SCI usually results in a diffuse damage zone of the spinal cord extending for 2–3 segments clinically reflected by a "zone of partial preservation." In incomplete SCI the distribution and extent of segmental damage are of great relevance for recovery. Contusion injuries inherently represent the combined damage of both segmental central and peripheral neural structures [22]. Preserved function of neuronal circuits below the level of the lesion is the target of rehabilitation training. Next to severity and completeness of the injury, clinical spinal syndromes are relevant as they can show distinct patterns of recovery due to specific epidemiology and anatomical distribution of lesion load in the spinal cord [23].

The *anterior cord syndrome* (ACS) due to a flexion injury of the spine results in predominant damage of the ventral cord, segmental ventral horn cells, and spinothalamic and long motor tracts. This is also possible when a minor mechanical impact triggers a disturbance of the blood supply from the anterior spinal artery [24]. In patients with diffuse non-penetrating spinal injuries, the clinical syndrome is characterized by segmental flaccid paresis and spastic paresis with disturbance of pain and temperature sensation caudal to the lesion level but sparing of light touch and proprioception which are mediated in the dorsal tracts of the cord. Incidence is low accounting for only 2.7 % of all traumatic spinal injuries [25] and less than 1 % of all spinal syndromes [23]. A series of patients undergoing cordotomy to cure otherwise untractable pain [26] showed that bilateral spinal damage anterior to the equatorial plane has little effect on the motor and functional performance of the patients who usually recovered from minor deficits within weeks. The difference between the patients

described by Nathan and those with a traumatic anterior spinal injury is due to the diffuse and extended nature of traumatic spinal damage as opposed to the anatomically precise anterior transection of the cord. Unlike a diffuse anterior spinal concussion, surgical dissection anterior to the equatorial plane will leave the lateral corticospinal tract unaffected and thus result in largely preserved motor control. Conversely, traumatic ACS as defined by Schneider [27] affects the anterior two thirds of the cord and hence involves damage of the lateral corticospinal tracts. This is associated with a poor prognosis and minor recovery rates of muscle force and poor coordination.

Traumatic *central cord syndrome* (CCS) is the most common acute incomplete cervical spinal cord injury accounting for 44 % of all spinal syndromes and for 9 % of all SCI in a recent study of 839 spinal cord injuries [23, 28]. About 20 % of patients with cervical spinal cord injuries present a clinical CCS [28]. The syndrome is characterized by predominant upper extremity weakness and clumsy hands and less severe lower extremity dysfunction and sensory and bladder dysfunction. It represents the oldest age group with the lowest admission functional level of all SCI clinical syndromes, which is a cofactor in determining relatively poor recovery of hand function in this group, despite its generally favorable outcome compared to traumatic incomplete cervical SCI in general [23]. CCS was originally thought to result from posttraumatic centro-medullary hemorrhage and edema [29] or from a Wallerian degeneration, as a consequence of spinal cord compression in a narrowed canal [28]. The central focus of spinal damage in combination with the special somatotopic organization of the corticospinal tract, where motor tracts for the upper are localized more centrally than those for the lower extremities, was assumed to be responsible for the predominance of motor deficits in the hands in CSS. However, more recent anatomical analysis and primate animal studies rather suggest that the syndrome is due to the specific effects of a cervical spinal lesion on direct corticomotor (pyramidal) tracts given their significant role in manual motor control [30]. This would be in line with the seminal findings of these direct corticomotoneuronal projections by Bernhard and Bohm [31] and with these authors' appreciation and consideration of this anatomical feature which is unique in primates and humans. A loss of the capacity for "fractionation" of movements and control of small groups of muscles in a highly selective manner [32] is as much characteristic of CCS as an impairment of the acquisition of new motor skills [33]. Therefore, when considering the significance of direct corticomotoneuronal control in human manual dexterity [30], CSS may be considered a prototypical condition where spinal cervical lesion inflicts damage predominantly on pyramidal tract axons affecting fine motor control and coordination of the hand. Furthermore, due to a different age distribution of the majority of patients with a cervical lesion as compared to CSS patients and, consequently, due to differences in admission functional level between these groups, the course of recovery is dependent on age as a cofactor to a significant extent.

A hemisection of the cord leads to *Brown-Séquard syndrome* (BSS), which was first described in 1851 by the neurologist Charles Edouard Brown-Séquard [34] as ipsilateral ataxia and paresis due to proprioceptive and motor loss in association with contralateral loss of pain and temperature sensation below the level of lesion. A surgical unilateral lesion dividing most of the ipsilateral tracts of the spinal cord

resulted in complete flaccid paresis of the ipsilateral limbs only for a few hours after which voluntary movements began to reappear [26]. Within days after such a sharp lesion, patients were able to exert slow digital movements, and walking ability was attained within 2 weeks. Slow and feeble manual function recovered within less than 3 weeks of the operation. This indicates that recovery and redundancy in corticospinal control is not weak in human SCI but in the majority of traumatic SCI is observed to a much lesser degree than in the cases described by Nathan indicating that there must be extensive diffuse lesioning of spinal tracts. While mostly due to penetrating injury to the cord in its pure form, even BSS-like syndromes with more or less lateralization of lesion are relatively rare in Europe and account for less than 4 % of all traumatic SCI [23]. Nevertheless, they are relevant as prognosis is known to be most favorable among incomplete traumatic SCI [23, 35] particularly with regard to ambulation. Physiologically, recovery occurs in a rather characteristic order with proximal extensors prior to distal flexors on the more affected side and vice versa on the less affected side [35]. This is attributed to the unilateral (distal flexors) and bilateral (proximal extensors) distribution of preserved fibers and their recovery due to sprouting and formation of collaterals. The recovery is most likely owed to lumbar midline crossing fibers [36, 37].

Conus medullaris syndromes amount to 1.7 % and *posterior cord syndrome* to less than 1 % in the analysis of McKinley and coworkers [23]. Data on these groups are sparse. In general, spinal syndromes tend to need shorter rehabilitation length of stay, indicating that sufficient functional outcome is reached after shorter duration of rehabilitation, which is likely secondary to an incomplete pattern of lesion and high proportion of preserved spinal nerve fibers [23].

Neurological recovery after a spinal cord lesion can be attributed to mechanisms of functional compensation, neural plasticity, or repair [12] where compensation refers to changes in function that can be achieved without any change in the neurological deficit (e.g., by adapted movement strategies). Plasticity refers to mechanisms that involve a reorganization of neuronal circuits (e.g., as occurs during motor learning) and is induced in a use-dependent way meaning that improvements are specific for a respective trained task [38]. Next to sprouting phenomena, this can be based on the use of preexisting "silent" pathways [39]. Repair mechanisms entailing remyelination or regeneration and reconnection of damaged spinal tract fibers would be reflected by changes in spinal impulse conductivity. The evaluation of the relative contribution of each of these mechanisms has shown that subjects with complete SCI improved in activities of daily living unrelated to changes of the neurological condition (i.e., by compensation), while incomplete SCI resulted in a greater functional and neurological recovery, supposedly by means of plasticity and some regeneration and sprouting within the propriospinal network as could be found in animal models [10, 40, 41]. The latter may be assumed true also in humans as functional recovery in incomplete SCI was not related to any improvement of spinal conductivity, as reflected in unchanged latencies of evoked potentials [12, 42–44]. This also supports the assumption that functional recovery in traumatic SCI occurs by compensation mainly, especially in complete SCI. Conversely, it could be argued in the case of incomplete SCI that additional neural plasticity leads to a

greater functional improvement as compared to complete SCI. From animal work it is known that reorganization of spinal circuits occurs at various levels of the CNS involving collateral sprouting of spinal tract fibers and most likely synaptic plasticity [41]. This likely also involves propriospinal pathways [40]. Relevant repair and remyelination of damaged long spinal pathways cannot be assumed.

4.2.1 Acute Onset and Severity (Trauma, Ischemia): Spinal Shock, Recovery of Muscle Tone, and Motor Function

When describing the natural course of disease following SCI, it must be distinguished between pathologies with acute onset and those which result in slow alteration of the cord, e.g., due to tumor or other etiologies with increasing compression. Following an acute onset, there will be a phenomenon of a sudden loss of reflexes and muscle tone commonly referred to as "spinal shock." The term was introduced by Hall in 1840, who, in describing the sudden loss and recovery of reflexes, for the first time linked it with the term "reflex arc" [45]. Our present idea is that a flaccid motor paresis is observed immediately after acute onset of a complete SCI when there are no motor responses to external stimuli below the level of lesion. During the subsequent days and weeks, motor reactions to external stimuli gradually reappear in a more or less systematic manner [46]. The phenomenon of spinal shock remains an issue of debate and controversy. Due to involvement of the autonomous system in acute SCI, there is some overlap with cardiovascular symptoms, i.e., arterial hypotension and cardiac compensatory response. However, the terms should not be confused with hypovolemic shock as opposed to the truly "nervous condition" of lacking striate muscle tone [47] as this may lead to medical misjudgment and therapeutic mismanagement [48, 49]. The question of duration of spinal shock can be seen as a matter of definition of the delimiting type of motor reaction or reflex [47]. Depending on what is chosen as the distinguishing motor criterion, cessation of spinal shock may be assumed with the appearance of a "delayed plantar response" (DPR) which occurs within hours after SCI and persists for hours to a few days [50, 51]. If deep tendon reflexes (DTR) are chosen as the criterion, then duration of spinal shock is longer and will comprise several weeks. Following the appearance of the DPR, reflexes tend to return in a sequence: bulbocavernosus, cremasteric, ankle jerk, Babinski sign, and knee jerk. Thus, the pattern of recovery appears to be cutaneous (polysynaptic) reflexes before DTR [46]. With regard to this clinical presentation, four phases of spinal shock have been postulated which are presumably paralleled by distinct pathophysiological processes. This has been postulated from clinical observations which were related to animal experiments [46]. However, it has to be pointed out that animal models of spasticity are rare and not well established as they may not relate to pathophysiology in the human [52]. When assuming some similarity between the rat animal models [53, 54] and the human, the following phases can be distinguished. Hyperpolarization of spinal motor neurons prevails during the short *initial phase* of areflexia (day 0–1). This is followed by the *second phase* with return of polysynaptic (cutaneous) reflexes (days 1–3) while DTR are

still lacking. Pathophysiologically this phase is characterized by denervation supersensitivity and receptor upregulation. During the *third phase* (days 4–30), DTR return in the majority of patients and the Babinski sign may be present [55]. It is distinguished from the *fourth phase* (days 30–360) when hyperactivity occurs in cutaneous and DTR which now respond to minimal stimuli. The physiology of the latter two phases is dominated by synapse growth and short (phase 3) and long axon growth (phase 4) from intraspinal and segmental afferent sources replacing vacant synaptic endings from axotomized supraspinal neurons. Thus, the time course of gradual cessation of spinal shock is protracted because synapse formation after injury seems to be axon-length dependent as well as activity dependent and competitive [46]. Appearance of interlimb reflexes indicates late changes reflecting increased polysegmental spinal reflex excitability 6–12 months after SCI [56]. Competitive synapse growth originating from preserved long descending motor input [57] and segmental reflex inputs [58] is postulated as underlying the individual outcome and clinical presentation of recovery of voluntary motor control and spastic motor disorder [56]. Complete and incomplete SCI were claimed to be distinguishable by the extent and duration of spinal shock in several studies lasting only minutes to hours in "slight" injuries [50, 59]. Furthermore, response amplitude to tendon tap and reflex spread to adjacent segments are sensitive indicators of preserved supraspinal control over lower limb musculature in subjects with acute SCI and may thus be helpful for prediction of recovery [50].

In the clinical view, the transition from spinal shock to spasticity is a continuum of gradually increasing motor excitability [60] with characteristic changes in muscle tone, spasms, and short- and long-latency reflex excitability. Neurophysiological methods have deepened our understanding of underlying excitability changes in spinal circuits and peripheral nerves during this transition [61, 62]. During spinal shock, the loss of tendon tap reflexes and flaccid muscle tone is associated with low excitability of spinal motor neurons as tested by neurographic methods (F waves) and with a loss of flexor reflexes, whereas H reflexes can be elicited. Reduced excitability of peripheral mixed nerves was based on high threshold stimulus–response relationships which were apparent from the early phase of spinal shock. This coincided with depolarization-like features reaching a peak after 12 and 17 days for the median and common peroneal nerves, respectively [46, 61, 62]. Between days 68 and 215 after SCI at the end of rehabilitation, these authors found that excitability for upper and lower limbs had returned toward normal values but not for all parameters. These changes of excitability of the peripheral motor axon are paralleled by the development of spasticity. During the transition to spasticity, the reappearance of tendon tap reflexes and muscle tone can parallel the occurrence of spasms and is associated with the recovery of excitability of spinal motor neurons as indicated by increasing F-wave persistence and flexor reflex excitability [60]. At later stages (2–6 months after SCI), clinical signs of spasticity can evolve. While little change in spinal excitability occurs after this transition phase, a decrease in compound muscle action potentials (CMAP/M-wave) and reduced flexor reflex amplitude suggest a secondary degeneration of spinal circuits and motor neurons subsequent to severe spinal trauma [60, 62, 63]. Furthermore, flexor

reflex excitability depends on the level of lesion, indicating that spinal interneurons and premotoneuronal circuits may depend on the extent of infralesional intact spinal network [50, 60].

4.2.2 Subacute and Chronic Spinal Cord Injury: Slow Adaptation, Compensation, and Causes of Deterioration

Subacute onset or chronic progression of a spinal cord injury may initially be associated with minor clinical symptoms and functional deficits as compared to acute traumatic lesions. Large-scale reduction of the spinal canal by tumor or degenerative stenosis with consecutive compression of the cord can go unnoticed for a long time period speaking to a remarkable capacity of the spinal cord nervous tissue for adaptation and compensation. Often sole symptoms will be spasticity below the level of spinal compression or lesion and resulting impairment of fine motor control with limb ataxia [64]. Other signs from the patient's history such as calve or thigh muscle cramps, subtle ataxia of gait and unexplained falls, discrete signs of bladder and bowel dysfunction such as urgency or residual volume after micturition may complement the impression of suspected spinal cord compression. Typically, spinal shock does not occur in cases with slow development of spinal cord injury. Local pain and segmental at- or below-level sensory loss may point to the level and anatomical location of a spinal lesion [65, 66]. Sensory loss may be limited to pain and temperature sensation, so-called dissociation of sensory loss. Therefore it is important to do segmental tests of both, pain and light touch in the clinical examination. Neurophysiological testing with motor and sensory evoked potentials of long spinal tracts reveals local demyelination with a significant slowing of the signal. Clinical and neurophysiological motor and reflex testing may reveal single impaired myotomes at the lesion level. In cervical canal stenosis with cord compression, e.g., secondary to spondylosis, without clinical evidence of myelopathy, clinical or electrophysiological evidence of cervical radicular dysfunction or central conduction deficits seems to point to a higher risk for developing myelopathy [67]. In case of symptomatic cervical spondylotic myelopathy, there are no specific patient or disease characteristics which have been shown to predict progress reliably [68]. However, clinical and/or electrophysiological evidence of cervical radiculopathy (or, more likely, ventral horn damage as indicated by pathological electromyogram at the affected segment) has been shown to predict progression [68]. Accordingly, contact heat evoked potentials are most sensitive in detecting anterior spinal lesions in cases of incomplete spinal cord damage [69]. These tests can be applied in addition to MRI scans to detect incipient myelopathy and help localizing pathology and planning therapy.

There are few acquired diseases of the spinal cord which can result in slowly progressing spinal cord damage if overlooked, among them vascular malformations. Spinal dural arteriovenous fistula (sDAVF) is the most common spinal vascular malformation representing 80–85 % of spinal cord shunts [70]. They may be underdiagnosed and bear a risk to be found late due to sluggish onset [71] and progression with time [72]. As a devastating endpoint, necrotizing myelopathy was

originally described following subacute onset with vascular hypertrophy and central myelopathy due to venous ischemia by Foix and Alajouanine [73]. The majority of patients are only diagnosed 10–15 months after onset of symptoms [74, 75], likely because symptoms are nonspecific in the early stages, leading to initial misdiagnosis. However, if left untreated, the disease will likely progress to serious morbidity, associated with slowly progressive myelopathy due to venous hypertension. Typically, feeding radicular arteries will increase venous pressure in lower thoracic and lumbar spinal cord leading to local reduction of arteriovenous pressure gradient and, hence, to change of spinal perfusion, wall thickening, and tortuosity of radial veins. Subsequently, this chronic venous hypertension and stagnation result in progressive edema and myelopathy [71]. Radicular veins in the lower thoracic and lumbar cord are fewer and smaller in caliber, and drainage is convergent rather than divergent as in the cervical region [71, 76, 77]. Consecutively, the lower thoracic and lumbar spinal cord is more vulnerable to such hemodynamic changes, and the initial symptoms thus usually reflect dysfunction of the lower spinal cord, typically presenting with bladder and bowel dysfunction such as incontinence or urinary retention, and erectile dysfunction at time of diagnosis [74, 75]. Earlier symptoms are more nonspecific and may include tingling below the level of lesion, neuropathic pain, gait disturbance or weakness, burning back pain or pain of the feet, and cramping. Due to the aforementioned anatomical particularities, sDAVF does not present in the cervical region and neither are they associated with traumatic cause or spondylotic degeneration [74]. Acute deterioration sometimes may commence with exercise, prolonged standing, changing position, or other maneuvers causing pressure alteration within spinal perfusion mimicking anterior spinal artery symptoms [74]. The majority of patients become symptomatic in middle age with male predilection [74, 78, 79]. As opposed to much rarer spinal arteriovenous malformation (AVM), sDAVF is never located within the spinal parenchyma, and patients are older and rarely suffer intramedullary hemorrhage [78]. It is important to realize that spinal arterial malformations should be excluded in case of suspicion using MR angiography or conventional spinal angiography as, ultimately, they are treatable diseases and hence should be detected early before progression will likely follow with irreversible myelopathic damage.

Subsequent clinical and functional deficits after treatment such as embolization of AVM or removal of a tumor or stenosis can be limited and depend on the degree of axonal damage inflicted on the cord by the compressing agent or during removing surgery. Removal primarily aims at preventing deterioration rather than functional improvement since myelopathy does not recover. As surgery of a highly compressed cord inflicts microtrauma and may cause local edema and bleeding, functional loss may be increased perioperatively, and the patient should be prepared and scheduled for rehabilitation. Although myelopathy is permanent, some functional recovery can be observed in the condition of cervical spondylotic myelopathy [80]. Typically the course of recovery and prognosis depend on the underlying general disease and on the time point, when the diagnosis of spinal compression is made and surgical removal can be accomplished. Functional recovery often requires weeks to months of rehabilitation for ataxia, paresis, spasticity, and bladder and bowel dysfunction.

Clinical presentation of spinal syndromes associated with tumors (see also chapter 7) is largely independent of the underlying histology and pathology. It may be indifferent for extradural, intradural, and intraspinal tumors. Back pain may be the leading clinical complaint indifferent of age group and etiology [65, 66, 81]. While treatment of the underlying tumorous process is most relevant in terms of general prognosis of the disease, prognosis and the concept of rehabilitation for spinal cord damage are similarly based on completeness and level of injury as discussed for traumatic cases.

The spinal cord is known to be the locus of a limited number of infectious and noninfectious inflammatory processes which may cause more or less selective destruction of neurons and tracts of the white matter or of a combination of both (see also chapter 6). Pathologically it may be possible to distinguish viral, bacterial, fungal or parasitic, and noninfectious inflammation such as caused by granulomatosis, paraneoplastic, or parainfectious processes or in conjunction with vasculitis and collagenosis such as Lupus erythematodes. Inflammatory processes of the spinal cord, whether infectious or noninfectious, often take a subacute or chronic course so that postinfectious and disseminated myelitis as well as viral myelitis may be associated with some deficits but with a generally favorable prognosis which overall depends on the extent of neuronal and axonal damage inflicted on the cord. Different types of viral inflammation are known to affect different anatomical areas of the cord. Anterior manifestation is seen with poliomyelitis and other enteroviruses, while other neurotropic viruses such as varicella show preponderance of the dorsal cord including sensory ganglionitis. Human immunodeficiency virus can lead to a vacuolar myelopathy of the thoracic cord with slow onset of asymmetric paraparesis which is often obscured by polyneuropathy. Subsequently, the clinical picture and course of such diseases will be characterized by selective neurological deficits often followed by slow recovery over weeks and months with persistent deficits.

Exemptions to these subacute and chronic courses of disease may be postulated for few etiologies which can present as acute necrotizing transverse myelitis, a condition occurring with some preponderance in young adults. Other exemptions with more acute onset include acute viral myelitis such as varicella and herpes simplex type I, Epstein-Barr virus, cytomegalovirus, poliomyelitis acuta anterior, spinal manifestation of early summer meningoencephalitis (ESME), and autoimmunologic pathology such as in neuromyelitis optica (NMO). Since these can be associated with significant vascular, perivascular, neuronal, and axonal damage resulting in necrotizing myelitis, sequelae may be significant, and prognosis for outcome can be limited. High age may be a relevant cofactor for a poor prognosis which is especially found in ESME where prognosis is poor for infections in the elderly and with spinal manifestation [82]. NMO may show recurring courses but usually all of the abovementioned present as single events of spinal inflammatory injury.

Myelitis secondary to bacterial, fungal, and parasitic granulomatous infections may present together with signs of a more generalized disease process. Prognosis largely depends on early onset of antibacterial treatment. The spinal lesion can primarily involve the pial and arachnoidal space whereas dural and epidural affection leads to abscess with consecutive focal compression, inflammation of local vessels, ischemia, and infarction. Chronic meningeal inflammation may provoke progressive pial constrictive fibrosis with local or disseminated strangulation of the

neighboring cord and cyst formation within the spinal canal, so-called spinal arachnoiditis. This is also found after spinal subarachnoidal bleeding. Changes within the nervous tissue ensue and scarring of the entouring meninges may thus cause secondary damage. This may comprise sequelae such as intraparenchymal cyst formation and syringomyelia as well as disturbance of spinal fluid circulation. While independent of the initial damaging cause, they often show protracted and recurring courses which present with fluctuation of motor function and states of segmental and remote neuropathic pain. These impairments of function can be related to local disturbance of spinal fluid circulation and to fluid retention with secondary compression of neural tissue. Thus, surgical drainage of cysts or syringomyelia is the treatment of choice [83, 84]. Unfortunately, benefit comes with the risk of further deterioration and loss of function and with the likelihood of recurrence of cyst formation. Therefore, decision for surgery to accomplish drainage of such cysts should be made with caution and based on clinical proof of deterioration of pain and function. Cordectomy can be a useful ultimate instrument in cases of deterioration to preserve functions of the upper extremities and to improve spasticity and pain in patients with severe myelopathy and tethered cord, syringomyelia, or arachnopathy of various etiologies [85]. Neurophysiological assessments should be performed in addition to MRI follow-up. Of note, any sign of secondary deterioration of the functional level of performance, incidence of new pain or sensory loss, change of the clinical level of lesion, or motor score and spasticity should lead to further diagnostic assessment for the abovementioned reasons.

4.3 Anatomical and Physiological Adaptations After Traumatic SCI

Spinal cord injury is associated with widespread changes upstream and downstream of the lesion site. They can be found remote from the lesion and affect both the central and peripheral nervous systems. They are related to immediate changes in excitability and connectivity of the somatosensory circuitry followed by use-dependent neural plasticity. Changes have been described at the cortical, subcortical, brainstem, spinal, supralesional, and infralesional level. Typically these changes affect the white matter of the spinal cord [86, 87] and likewise the white and gray matter of the brain, expressing remote atrophy due to deafferentation and deefferentation [88–91]. The following section describes these changes with respect to their time course, physiological systems, corresponding anatomy, and assumed underlying mechanisms.

4.3.1 Supraspinal Adaptations, Sensory and Motor System Reorganization

4.3.1.1 Sensory

Functional reorganization of sensory cortex has first been described in classical amputation experiments in monkeys where cortical sensory topographic maps were gradually changed with significant shift and reorganization of the primary and

secondary afferent cortices [92, 93]. The cortical area deprived of its original input was activated by stimulation from adjacent body regions. Similar changes have been shown in SCI animal and human investigations using a variety of experimental approaches. Studies using functional magnetic resonance imaging (fMRI) based on alterations in blood oxygenation level (BOLD) showed that in rats stimulation of the forelimb results in enhanced regional blood flow in the corresponding cortical sensory area 3 days after acute complete thoracic transection [94]. Similar changes in primary sensory cortex were found in chronic humans after complete thoracic SCI [95]. Expansion of inputs from the adjacent non-affected body areas was confirmed with methods comparing fMRI with retrograde tracing techniques [96] and neurophysiological techniques [94, 97]. The process of sensory reorganization commences within minutes to hours of the spinal lesion as shown in animal experiments [97] with consecutive changes lasting weeks to months [91, 98] and at least up to 1 year in humans [42, 44]. Studies in several animal species have confirmed that cortical and subcortical reorganizations have a crucial part in functional recovery [9, 99]. The process of reorganization is dependent on the severity of the lesion, showing different recovery periods and outcome patterns after an incomplete, as compared to a complete spinal lesion [98]. Adaptations involve a network of upstream somatotopically related brain regions in animals and humans [100–102] which can be adversive or dysfunctional, e.g., resulting in neuropathic pain. Immediate functional reorganization comprises an early increase in excitability of cortical areas representing the unlesioned limb cranial to the level of lesion [95, 97] accompanied by a slowing in spontaneous brain activity [97, 103]. The latter has been attributed to a loss of thalamocortical input following deafferentation [104] termed thalamocortical dysrhythmia [105] which is not confined to the affected sensory area. A relationship of these phenomena of cortical excitability change and long-term reorganization with neuropathic pain has been a matter of debate [102, 106, 107], but a conclusive pathophysiological concept is still missing.

4.3.1.2 Motor

Functional reorganization is not limited to sensory areas following SCI. Reorganization and degenerative processes likewise affect ascending and descending tracts severed by spinal injury [89, 101, 108]. Primary sensory cortex may make increased contribution during recovery of hand function after SCI [109, 110]. Yet a widespread network of sensorimotor areas seem to undergo changes following SCI [100] with a sequence of alterations related to the phases of reorganization. This will cause signal shifts and intensity changes which are much dependent on the technology of investigation. Of note, fMRI and metabolic imaging of the brain, such as positron emission tomography (PET), will not be sufficient to unravel the underlying neurophysiological mechanisms of sensorimotor reorganization. While it has been demonstrated that BOLD reflects local neurophysiological plastic processes of the brain [111] also related to SCI [112], metabolic signal changes cannot distinguish between excitatory and inhibitory neurophysiological activity, nor are they specific for sensory- or motor-related activation. For instance, PET signal changes have been found in bilateral primary motor cortex in primate recovery from incomplete cervical

lesions. However, ipsilateral M1 did not prove essential for functional recovery when testing with temporal cortical inactivation [113]. The same series of experiments could show that contralateral primary motor cortex and premotor areas make time-variant contributions to recovery of digital movements with increasing contribution of secondary motor areas during later stages of recovery. A dramatic temporal change of the contra-lesional cortical primary hand representation area was described by studies showing an early intrusion of face or proximal body parts, followed by progressive reappearance of digital representation during the subsequent phase of digital movement recovery, as could be shown by intracortical microstimulation [114]. Such tests are not amenable to the human. However, corticomotor representation of forearm muscles similarly was shown to change in human SCI where hand movement-related BOLD signal shift toward the cortical leg representation area did not coincide with the posterior shift in the hand motor output map as tested by transcranial magnetic stimulation [89, 115]. Reorganization within the primary cortical and corticospinal hand areas and contributing cortico-cortical input are the most likely contributors. Increased motor thresholds [89] and initial lack of excitability of corticospinal fibers spared by the spinal lesion [114] indicate that following cervical SCI, the contralateral primary motor cortex requires reorganization involving adjacent secondary areas to sufficiently increase corticospinal projections to warrant functional recovery of digital movements [88, 114, 116].

While reduced corticospinal excitability has been shown for the cortical motor areas of the limbs affected by spinal lesion [89], an increase in excitability of corticospinal projections is found to non-paralyzed muscles above the lesion [116]. At this point, the combination of fMRI and even navigated focal cortical stimulation studies fail to localize or explain the mechanisms responsible for functional motor recovery.

Novel MRI sequences provide surrogate markers of directional organization within CNS parenchyma. Diffusion tensor imaging (DTI) is a novel technique to determine if SCI in humans results in anatomical changes within sensorimotor cortices, subcortical areas, and descending motor pathways. With morphometric and DTI methods, loss of gray matter volume in the primary motor cortex, medial prefrontal, and adjacent anterior cingulate cortices was shown for complete SCI subjects together with structural abnormalities in the same cortical areas, in the superior cerebellar cortex, and in the corticospinal and corticopontine tracts [101]. Onset and time course of these changes was rapid, showing decline of white matter in the cranial corticospinal tracts at the level of the internal capsule and cerebral peduncles within weeks of SCI [88]. Rapid and progressive up- and downstream spinal tract atrophy is related to cortical and subcortical atrophy and to functional disability [88, 115, 117]. Cortical gray matter thickness is reduced in the representative sensorimotor areas, and this is related to functional impairment [115], suggesting retrograde corticospinal degeneration [116]. Therefore, early extensive upstream atrophic and microstructural alterations within corticospinal axons and sensorimotor areas which are related to functional outcome must be assumed in SCI. The use of myelin-sensitive magnetization transfer (MT) MR sequences, as well as the time course showing initial significance of white matter atrophy within 40 days after spinal

trauma, corresponds to the time course of myelinated axons undergoing atrophy as would be expected with Wallerian degeneration [88]. The rate of spinal cord atrophy was unrelated to the level of lesion, thus suggesting distance-independent degeneration induced by trauma. Next to established clinical and neurophysiological tests, novel microstructural imaging techniques are therefore promising tools to complement the understanding of supralesional reorganization. Together with clinical and neurophysiological assessments, the sensitivity to detect individual changes may be further increased. The description of the time course of these adaptations comprising degeneration and reorganization will help to improve prognostication on the single subject level and detect true regenerative processes in pending clinical trials.

4.3.2 Brainstem and Spinal Adaptations

Functional reorganization and recovery after human SCI are almost exclusively described in the sensorimotor cortex (see previous paragraph, for review cf. Nudo, [118]). Ample information is available about spinal atrophy of corticospinal and bulbospinal and ascending projections [86, 87, 119] as well as about intraspinal networks [120]. However, little is known about adjustments following an SCI manifesting in the brainstem, which contains the phylogenetically old and functionally most important centers for basic control of complex movement [121]. Key structures for the initiation and execution of locomotion are located in the midbrain, pons, and medulla oblongata [122]. Locomotor command regions are located in the rostral brainstem such as the mesencephalic locomotor region (MLR). From animal studies it is known that they directly connect with bulbar output systems, for instance, the medial reticular formation [123–125]. The latter, in turn, projects to the spinal cord to initiate, modulate, and coordinate limb movements and postural support during locomotion, while locomotor rhythm is produced by the spinal central pattern generators [124, 126–128]. While these systems are known to be similarly organized in all vertebrates, there is scarce information on some of them in the human. For example, the rubrospinal system is known to be involved in the execution of precise limb movements during postural responses in non-primates [129, 130], while its role in primates seems to relate to cooperation with the pyramidal tract in producing skilled manual movements [41] yet, according to Nathan and Smith [131], may not reach the cervical enlargement in humans. In quadrupedal animals vestibulospinal tracts primarily control balance and posture [129, 132, 133]. Although these phylogenetically conserved brainstem systems form crucial components in the central motor control network, information on reorganization following spinal injury is limited [41]. Recent animal work on brainstem plastic reorganization following cervical SCI presents evidence of significant and extensive sprouting and infralesional midline crossing originating from gigantocellular reticular formation [121]. It must be kept in mind that these results cannot be transferred directly to human SCI. However, detailed descriptions of rapid recovery within hours of anterior and anterolateral cordotomies in humans done for pain relief and their postmortem comparison indicate similar bilateral distribution of

these pathways with a preponderance of ipsilateral fibers [86]. This may point to the possibility that reticulospinal projections to the spinal gray matter play a significant role in functional recovery [26, 86, 87]. Given the phylogenetically conserved role of these brainstem centers and tracts for motor control [124], this analogy in anatomy and the immediate recovery within hours after a cervical hemisection suggests that unmasking of redundant descending systems prior to sprouting is among the effective mechanisms which play a role in recovery following human SCI, as is true in other mammals. Within weeks after cervical hemisection in rats, there was evidence of anatomical plasticity of spinal descending tracts which was paralleled by considerable recovery of motor function of the hindlimbs to a larger degree than in the forelimbs. It was associated with bulbo-reticular adaptations, and the effects of functional recovery were immediately extinguished by lesioning the reticular gigantocellular nucleus from which the sprouting had originated [121]. This pattern of lesion and subsequent recovery shows much similarity with a typical human Brown-Séquard lesion in its rostral-caudal gradient of improved motor function with a predominance of locomotor recovery [35]. One substrate of functional recovery seems to be the additional formation of cervical and lumbar midline crossing fibers [9, 37] which are shown to constitute a characteristic feature of reticulospinal pathways [121]. While there is a clear notion that corticospinal projections may have more relevance for the recovery of manual dexterity, the underpinning of the latter study is that brainstem plasticity may have more significance in functional recovery of the lower extremities than has been acknowledged to date.

Few neurophysiological studies are available on adaptations at the brainstem level following SCI in humans [134–136]. The functional anatomy of the brainstem reflex pathways allows a differential testing by specific brainstem reflex excitation and neurophysiological recording [137–140]. This is commonly used in clinical neurophysiology as it allows a differential localization of pontine, bulbopontine, and reticulo-pontine malfunctioning and lesion. The classical tests comprise blink reflex (pontine, early R1; bulbopontine lateral reticular formation and spinal trigeminal nucleus, late R2 components projecting on the facial nucleus to effect activation of the orbicularis oculi muscle [138, 139]), its prepulse modulation, the auditory startle reaction (via the auditory nerve, cochlear nucleus, and nucleus reticularis pontis caudalis, through reticulobulbar and reticulospinal tracts; [141, 142]), and masseter silent period (bilateral oligosynaptic midpontine circuit [143, 144]). Modulation of these reflexes can be tested by double-pulse paradigms such as prepulse inhibition of the blink reflex which is an operational measure of sensorimotor gating [134]. All of the above show a SCI-related disinhibition which is reversible with baclofen suggesting GABAergic involvement. While these effects point to little differential influence on motor or functional recovery, they may most likely be associated with increased brainstem-mediated reflex excitability and with spasticity [134] in an incomplete spinal lesion. The time course and onset of these alterations following an SCI is not known.

Electrophysiological testing of vestibulospinal input to postural control in incomplete SCI was shown by galvanic vestibular stimulation (GVS) [145, 146].

This has been suggested as an addendum to clinical examination. As GVS induced responses in sway and muscle responses were reduced compared to controls, it was concluded that modulation of vestibulospinal control in incomplete SCI is impaired.

4.3.3 Peripheral Adaptations

Spinal injury is a prototype of the combined occurrence of a central and peripheral motor syndrome. Cervical and lumbar spinal lesions inevitably involve not only long and short tract spinal fibers but also dense populations of motor neurons and roots over two to three segments supplying arm and leg muscles, respectively. Therefore, a significant part of the segmental motor deficit is attributed to the collateral damage of the peripheral motor neurons of the anterior horn resulting in permanent flaccid paresis [147, 148]. Motor neuron and ventral root damage generally have a poor prognosis [149–153]. Thus, at the lesion level, there is an increased likelihood for persistent weakness as a result of spinal motor neuron damage in addition to central impairment induced by damage to long descending tracts.

Despite the prevailing view that lower motor neuron function below the spinal lesion level remains relatively intact after SCI, there are clear indications of substantial effects of an SCI on peripheral motor neuron function. A growing number of studies show that this affects spinal motor neurons as well as their peripheral axons [60–62, 154]. Peripheral nerve deficits in cervical or thoracolumbar SCI can be assessed by neurographic, electromyographic, and reflex recordings. The differentiation of flaccid paresis due to spinal shock and ventral horn damage after SCI can be distinguished by these techniques [22]. Decentralization after SCI had significant effects on lower limb axons, not attributable to direct trauma as remote effects were shown for cervical spinal lesion on lumbar ventral horn motor neurons [62, 154]. These effects were slow in onset and showed differential time courses in the upper and lower extremity motor neurons remote from and below the spinal lesion, and a dependency was observed on the severity of SCI [62]. Likewise, as an effect of adaptation of motor function subsequent to SCI, excitability of infralesional motor axons was shown to change remote from the lesion site [61]. These authors used threshold tracking techniques and peripheral nerve conduction recordings in a longitudinal approach comparing healthy subjects and acute traumatic SCI and related results of peripheral motor axon excitability to clinical measures of strength and serum electrolyte samples. Amplitudes of peripheral nerve compound motor action potentials were reduced, consistent with axonal loss, and if excitability changes were more prominent the more severe the SCI with a progressive deterioration over time [62]. These changes were only observed in peripheral nerves originating below the spinal level of lesion where it was difficult to activate these nerves electrically. Systemic proinflammatory upregulation and inflammatory responses or a general shift in serum electrolyte levels were ruled out as possible causes due the fact that supralesional nerves remained unaffected. While still not fully understood, these changes in the infralesional peripheral motor system may be seen in

the context of transsynaptic degeneration or dying back processes based on previous animal studies [62, 155, 156].

Contrary to prevailing opinion, these recent data demonstrate that significant reduction in peripheral motor axonal excitability occurs early during spinal shock which is unrelated to systemic humoral or serum electrolyte changes after SCI. Decentralization and consequent inactivity of peripheral motor axons seem to underlie the remote axonal changes in excitability. Furthermore, following initial excitability changes, subsequent further deterioration in axonal function may be seen before recovery ensues, and this recovery may be incomplete [61].

4.4 Time Course of Clinical and Functional Adaptations

After a spinal lesion, depending on severity and lesion level, motor and functional recovery begins in parallel with cessation of spinal shock and an increase in muscle tone. Characteristic recovery curves have been obtained from large databases pooling information on SCI according to standardized protocols [11–14]. These have informed health professionals about typical time course of recovery of sensory and motor function below the level of lesion.

4.4.1 Motor and Functional Recovery

Recovery of strength usually is steepest during the first 100 days after injury and then levels out within the course of a year, but late improvements are possible. Overall a considerable and significant improvement in motor function can be observed in paraplegic and tetraplegic subjects. The relative improvement (i.e., normalized to individual maximum potential recovery) of motor function is greater in incomplete than in complete SCI (ASIA Impairment Scale (AIS) A, tetra 14 ± 19 % versus para 7 ± 18 %; AIS B, tetra 24 ± 24 % versus para 30 ± 21 %; AIS C, tetra 63 ± 27 % versus para 58 ± 26 %; AIS D, tetra 73 ± 25 % versus para 67 ± 32 %) and greater in tetraplegic than in paraplegic subjects [12]. Motor paralysis in SCI in the chronic state is characterized by a lack of strength and velocity and may be additionally aggravated by overlaying spasticity. Other than stroke, SCI does not induce an impairment of dexterity [157]. Increasing amplitudes of motor evoked potentials during a 1-year follow-up after incomplete SCI indicate that repair mechanisms may play a role likely involving propriospinal networks and the peripheral nervous system [43, 62, 156, 158].

Another aspect of motor recovery concerns segmental changes (Table 4.1). Spontaneous neurological recovery of one to two spinal segments has been described within the first year after SCI [11, 14, 160]. This may be more relevant in terms of functional improvement and clinical outcome than improvement of motor score.

The time course of spontaneous motor recovery after a traumatic cervical sensorimotor-complete SCI is well known from various study populations. After 1

Table 4.1 Functional outcome as can be expected in motor-complete cervical SCI depending on lesion level

	C5	*C6*	*C7*	*C8*	*T1*
Muscles groups[a]	Elbow flexors	Wrist extensors	Elbow extensors	Finger flexors to the middle finger	Small finger abductors
Personal independence[b]	Type, feed	Drink, wash, shave, dress upper body	Turn in bed, dress lower body	Bladder and bowel care	
Wheelchair management[b]	Manipulate brake, push on the flat	Remove armrests/ footplates	Wheel over uneven ground	Negotiate curbs	Balance on rear wheels
Transfers[b]		From chair to bed or car	From chair to toilet or chair or bath	From chair to bath	From chair to floor

Taken from van Hedel and Curt [159]
A segmental change will have significant effect on the various levels of functional independence in activities of daily life
[a]From ASIA (2002) American Spinal Injury Association, Chicago
[b]Reprinted from Bromley (1998) Churchill Livingstone, Edinburgh, p 245

year, the average recovery amounts to 10–11 out of 50 bilateral upper extremity motor points [13, 160–162]. This is independent of cervical lesion level [162]. Cervical SCI patients with facet dislocation tended to present with a more severe degree of initial injury and displayed less potential for motor recovery at a 1-year follow-up [67]. Yet, it is important to note that a change in motor score cannot necessarily be taken as an indication of a gain in lesion level or functional independence. The distribution of gained motor points may be functionally more important than a given sum of improved motor points. Similarly, recovery of function is not exclusively dependent on recovery of motor score. Following traumatic SCI, there are no age-related differences in the recovery of motor score but significant age effects on the level of functioning [157, 163, 164]. The likelihood for a gain of one or two motor segments, which means a highly relevant improvement for a patient suffering from a complete cervical SCI, is 29–41 % and 29–33 %, respectively (Fig. 4.1), taking into account the data from two large cohort studies with more than 2600 patients together [162]. On the contrary, after 1 year, 60–70 % of subjects spontaneously recovered one motor level. Furthermore, these motor level changes were only moderately related to gains in motor score. However, a change of two motor levels in a cervical complete SCI was related to meaningful functional improvement as expressed by validated functional outcome scores [165], suggesting that careful tracking of cervical motor recovery outcomes and segmental changes

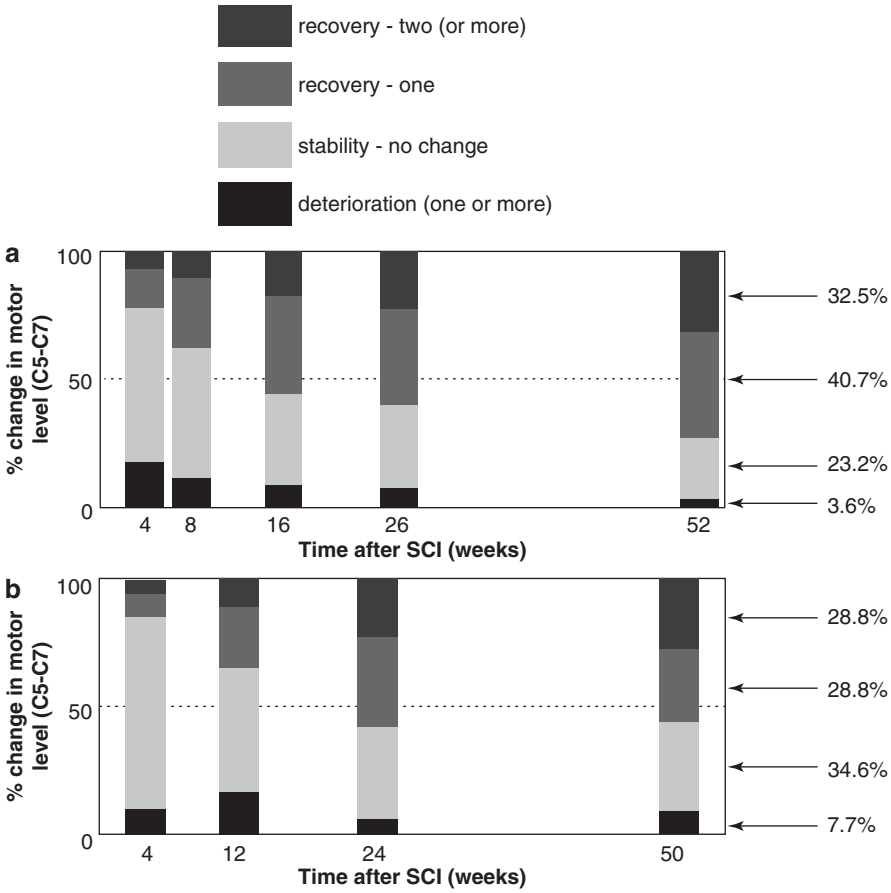

Fig. 4.1 Proportion of individuals with an initial C5–C7 motor level spontaneously deteriorating, remaining stable, or gaining motor levels from baseline to different time points over the first year after cervical AIS-A SCI [162]. The percentage of individuals in each category of motor level change or stability at 1 year after SCI is shown from (**a**) Sygen; (**b**) EMSCI [162]

may provide necessary sensitivity and accuracy to reliably detect significant *and* meaningful recovery of function or potentially as the equivalent of a significant treatment effect in this group of SCI patients [162]. Motor recovery in these patients showed a very characteristic time course with major improvement occurring within the first 12 weeks after SCI (Fig. 4.2). While these numbers are suggestive of characteristic recovery profiles, it has to be kept in mind that despite the rather large database these numbers are still too low to obtain recovery profiles in relation with lesion level.

A motor level deterioration is much more rare (4.6 %), is more prevalent in lower cervical lesions (C6 or C7), and usually occurs within the first 4–8 weeks. Other than in the cervical complete SCI, thoracic lesions do not show a similar motor improvement, most likely because they are not accessible by the standardized

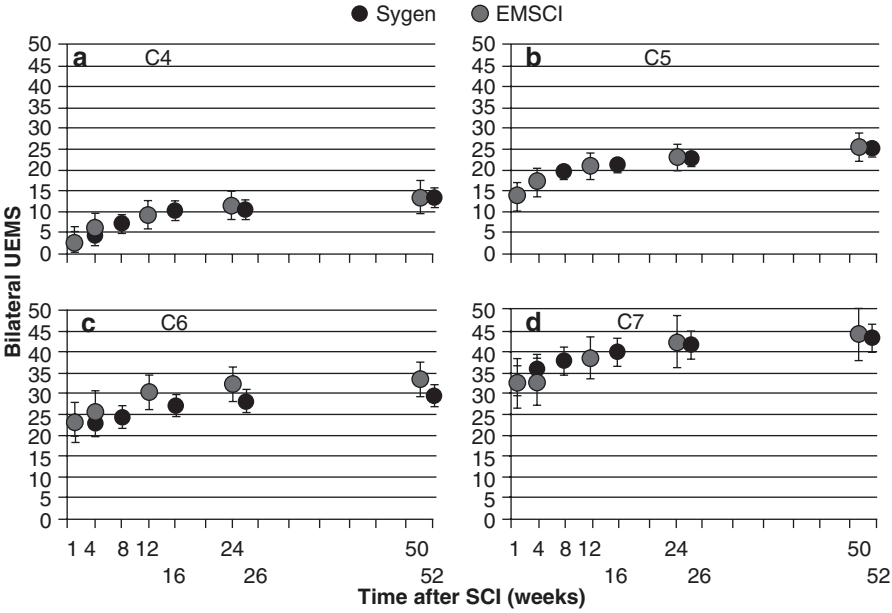

Fig. 4.2 Upper Extremity Motor Score (UEMS) during spontaneous recovery in the EMSCI and Sygen databases. (**a**–**d**), initial motor level of C4, C5, C6, and C7, respectively. (Error bars = 95 % confidence intervals) [162]

neurological (ISNCSCI) and functional (Spinal Cord Independence Measure; SCIM) tests [159]. Segmental changes in the thoracic region will be expressed exclusively in sensation changes in the ISNCSCI exam, and while trunk stability, arm force, and respiratory function may be better, the lower the level of thoracic lesion, this is not truthfully reflected by common clinical or functional standardized scores.

4.4.2 Sensory Recovery

Sensory improvement in traumatic SCI is poor. Only small significant improvements were found with differences between tetraplegic and paraplegic subjects but not between complete and incomplete SCI [12]. In a population of 460 acute traumatic patients, the light touch sensation increased significantly in tetraplegic AIS A and C subjects, whereas light touch sensation on average of all tested segments remained unchanged in most paraplegic patients. Pinprick was even more stable and only increased moderately in tetraplegic AIS C patients. In this context, it must be kept in mind that the course scale of pinprick and light touch (LT) assessment according to ISNCSCI may not be sufficiently sensitive and responsive to detect subtle changes

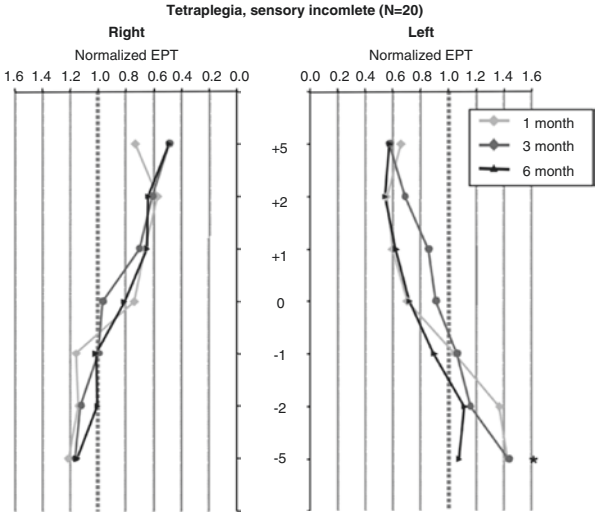

Fig. 4.3 Course of normalized electrical perception threshold (EPT) within the first 6 months in sensory-incomplete tetraplegia: Average EPT values at 5, 2, and 1 levels above the neurological lesion; at level; and at 1, 2, and 5 levels below the neurological level of lesion. The averages are presented for 1, 3, and 6 months after initially sensory-complete paraplegia. Normalized EPT values above 1 indicate pathological EPT values. Abbreviations: *N* number of participants, *EPT* electrical perception threshold, normalized EPT is the recorded EPT value in spinal cord injury patients divided by the EPT value corresponding to the upper limit of the 95% confidence interval of the recorded EPT value in healthy participants in the dermatome being tested. $^{*}P \leq .05$, $^{**}P \leq .01$ [168]

during the course of recovery or in a clinical trial. For that reason there was much interest in introducing a methodology which would allow sensory segmental testing on a more sensitive parametric scale. In order to overcome these shortcomings of LT testing, the electrical perception threshold (EPT) was introduced as a highly standardized and scalable measure [166] and validated in the healthy and a group of SCI patients [166–168]. According to these studies, it was possible to obtain reference values for each dermatome between cervical 3 (C3) and sacral 2 (S2) and age- and gender-specific nomograms. The EPT was shown to add sensitivity and resolution to the standard clinical testing as it was possible to show specifically the reliability of the EPT for each individual dermatome in healthy participants and the sensitivity of the EPT in detecting changes over time (i.e., responsiveness) in patients with SCI [168]. Normal values for each segment are thus available introducing objective and standardized sensory testing into SCI assessment with anatomical nomograms and demonstrating minimal or no segmental change over time in complete and incomplete SCI patients at and below the level of lesion. Thus, irrespective of the type of assessment, very little spontaneous recovery of sensory perception can be found caudal to the lesion in SCI. The reason for this difference between the motor and sensory adaptations seen after an acute SCI is unknown (Figs. 4.3 and 4.4).

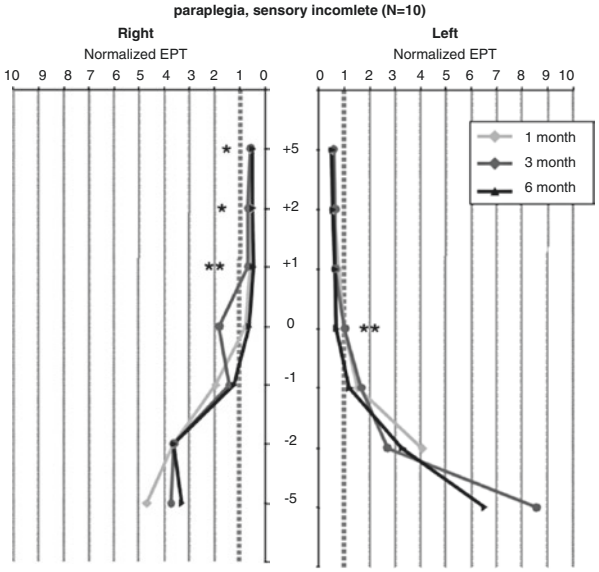

Fig 4.4 Course of normalized electrical perception threshold (EPT) within the first 6 months in sensory-complete paraplegia: Average EPT values at 5, 2, and 1 levels above the neurological lesion; at level; and at 1, 2, and 5 levels below the neurological level of lesion. The averages are presented for 1, 3, and 6 months after initially sensory-complete paraplegia. EPT norm values above 1 indicate pathological EPT values. Abbreviations as in Fig. 4.3. [168]

4.5 Outlook

As was discussed in this chapter, motor and functional recovery begin in parallel with cessation of spinal shock and increasing muscle tone following an acute SCI. Characteristic recovery curves for dedicated subpopulations have been obtained from large databases pooling information on SCI according to standardized protocols. For traumatic SCI these have informed health professionals about the typical time course of recovery of sensory and motor function below the level of lesion. Similar data is missing for nontraumatic etiologies, however. Recovery mechanisms as described in the previous paragraphs must thus be understood in the context of traumatic SCI only. Knowledge about the course of natural recovery may be useful to help design and evaluate incipient clinical trials to improve recovery in traumatic SCI. A key issue in this context is to distinguish treatment effects from natural recovery, in order to deal with the difficulty of determining potential efficacy of an intervention. In this context, knowledge of the disease course may not be sufficient, but additional assessment may be required, e.g., of underlying neurophysiological changes or surrogate markers such as MRI studies to fully characterize adaptations subsequent to a traumatic SCI in order to distinguish true treatment effects. This may help in the process of trial design and therapy development. Stratification and prediction strategies are crucial in this process as will be pointed out further in a later chapter.

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Part II

Non-traumatic Spinal Cord Injury

Spinal Cord Vascular Disease

5

Norbert Weidner

Abstract

This chapter describes the two main disease entities affecting the spinal cord vasculature, spinal cord ischemia, and spinal vascular malformation.

Spinal cord ischemia differs significantly from cerebral ischemia patients in terms of age, clinical presentation and course, risk factors, and underlying pathology. Clinical severity depends on the lesion extent and the lesion level. Recovery is most often incomplete and about 50 % of patients remain wheelchair bound. The etiology of spinal cord ischemia can be divided into three entities, all of which have different diagnostic algorithms, different preventive, acute/rehabilitative strategies and different outcomes: (a) spontaneous, (b) complication of an underlying acute disease, and (c) complication of aortic diagnostic/therapeutic procedures. Spontaneous spinal cord ischemia is often attributed to the typical cerebral ischemia risk factors. However, diagnostic workup needs to be broader including underlying inflammatory causes (infectious, parainfectious, autoimmune). At the same time, diagnostic imaging in the acute phase is more challenging compared to cerebral ischemia, which hampers efforts for acute therapeutic interventions such as thrombolysis. As further treatment option, in particular after aortic surgery, lowering of the intraspinal pressure by lumbar drainage to increase intraspinal perfusion pressure can be considered.

In most instances, spinal vascular malformations consisting of spinal dural arteriovenous fistulas, arteriovenous malformations, and cavernous angiomas cause a more slowly progressive disease manifestation as opposed to the sudden onset in spinal cord ischemia. The underlying pathophysiological mechanism is based on arterial blood shunted into perimedullar veins, which causes venous

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congestion in the spinal cord parenchyma. Depending on the type of malformation, effective neurosurgical and interventional treatment options are available. The prognosis heavily depends on an early diagnosis and treatment, which may allow to at least partially reverse neurological dysfunction.

5.1 Introduction

Both spinal cord ischemia and spinal vascular malformation are considered rare diseases. In case of spinal cord ischemia, exact epidemiological numbers are missing. According to the literature, spinal cord ischemia accounts for 1 % of all ischemic events within the central nervous system. In Germany, 196,000 first-ever ischemic strokes occur every year [1]. Based on this number, almost 2000 cases each year would suffer from spinal cord injury. Considering that the most frequent cause of para- or tetraplegia – traumatic spinal cord injury – already accounts for roughly 2000 new cases each year in Germany suggests that the incidence of spinal cord ischemia is much lower. However, exact numbers are missing. Likewise, the exact incidence of spinal vascular malformations is unknown. In various publications, the incidence for spinal dural arteriovenous fistulas, the most common type of spinal vascular malformation, is reported between five and ten cases per one million. The source for this estimate cannot be confirmed.

5.2 Vascularization

Knowledge about the arterial supply of the spinal cord is still far from being complete. Due to the small diameters of respective vessels (maximum diameter in the artery of Adamkiewicz is 1.2 mm; all other vessels are mostly in the range between 0.1 and 0.8 mm), precise in vivo studies are difficult. Most of our current knowledge related to spinal cord vascular supply is based on postmortem studies after microinjections of staining fluids and microradiological assessments [2].

During embryonic development the anterior spinal artery develops from the anastomosis of ascending and descending branches of 31 bilateral segmental anterior radicular arteries. In the adult, the majority of these segmental feeders of anterior spinal artery obliterate. Only around 6 of these feeders remain in the adult. Around 2–3 radicular arteries can be found at cervical level, 2–3 at thoracic level, and 0–1 at the lumbosacral level [2] (see chapter 2).

The vast collateral vascular network around and within the spinal cord – despite the fact that during development the majority of segmental arteries are obliterated – accounts for the rare incidence of ischemic events within the spinal cord. More recent studies in pigs clearly indicate the presence of a robust collateral network, which helps to maintain spinal cord perfusion even after interruption of relevant segmental arteries [3]. After infusion of acrylic resin and subsequent curing of the resin, the selectively visualized spinal vasculature shows extensive collaterals

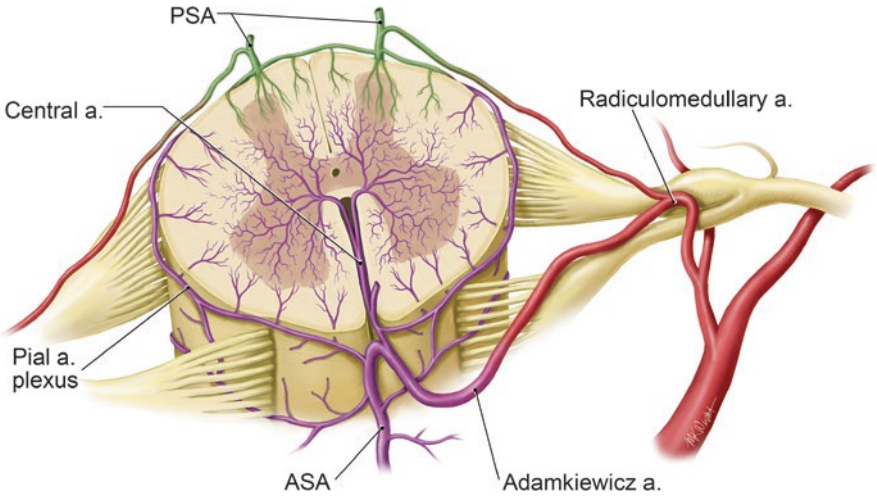

Fig. 5.1 Vascularization of the spinal cord: The main blood supply for the lower thoracic and lumbar spinal cord is derived from the Adamkiewicz artery feeding into the anterior spinal artery (*ASA*) [31]. The dorsal one third of the spinal cord receives blood supply through the posterior spinal arteries (*PSA*). The central arteries (*central a.*) provide the central vascular supply to the ventral horn, anterior portion of the dorsal horn and dorsal columns, the inner half of the anterior and lateral columns, and base of the dorsal columns in a centrifugal pattern. The pial arterial plexus (*pial a. plexus*, peripheral system) supplies the outer portion of the anterior and lateral columns and the posterior portion of the dorsal horn and dorsal columns in a centripetal fashion (Figure used with kind permission from Nicholas Theodore, M.D.)

between the segmental arteries feeding into the anterior spinal artery on the one hand and vastly interconnecting vessels outside the spinal canal supplying the erector spinae, iliopsoas, and associated muscle vasculature posteriorly on the other hand. Moreover, multiple longitudinal anastomoses along the vertebral column exist, which receive additional supply from the subclavian artery rostrally and the hypogastric arteries caudally [4]. According to the literature, such a comparably robust collateral vascular network exists in humans [3]. The rather few vessels providing spinal cord perfusion anteriorly versus the robust vessel network for the paraspinal muscles suggest that paraspinal muscle activity can impose a steal effect and thus threaten spinal cord perfusion.

The ventrally located anterior spinal artery and two posterior spinal arteries directly supply the spinal cord (Fig. 5.1). Along the length of the spine, these vessels receive input from the subclavian artery via the vertebral artery, the thyrocervical trunk, and the costocervical trunk. Furthermore, several segmental arteries from the intercostal arteries and the lumbar artery containing the arteria radicularis magna (artery of Adamkiewicz) feed into the spinal cord vasculature (Fig. 5.2). More caudally, the hypogastric arteries support the spinal cord through the lateral sacral and iliolumbar arteries. The artery of Adamkiewicz arises on the left side of the aorta between the T9 and L1 segments, to anastomose with the anterior spinal artery. The artery of Adamkiewicz is typically cranially oriented due to cranial movement of the spinal

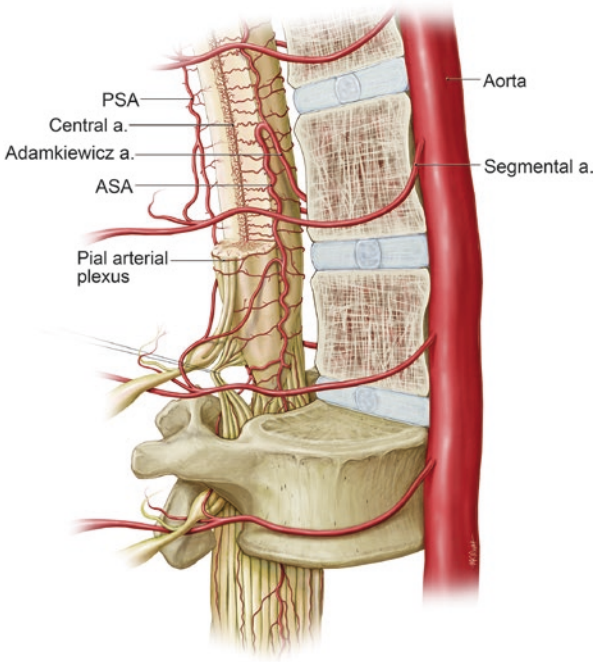

Fig. 5.2 Longitudinal organization of arterial blood supply in the spinal cord. Segmental arteries (*segmental a.*) derived from the aorta reach the spinal cord surface and form the anterior spinal artery (*ASA*) [31]. The largest segmental artery, typically located between the L1 and L2 level on the left, is termed great radicular artery or artery of Adamkiewicz (*Adamkiewicz a.*). Central artery (*central a.*), posterior spinal artery (*PSA*) (Figure used with kind permission from Nicholas Theodore, M.D.)

cord against the vertebral column. Once at the cord surface, the artery of Adamkiewicz branches into a small ascending vessel and a large caudally oriented vessel, which gets formed after a hairpin curve of the artery of Adamkiewicz. It supplies the lower two thirds of the spinal cord. Posterior spinal arteries supply the dorsal third of the spinal cord – mainly the dorsal columns. Central arteries provide the vascular supply ventrally in a centrifugal pattern (central system), whereas the pial plexus feeds into the cord into a centripetal fashion supplying more superficial and dorsal regions of the spinal cord (peripheral system). The pial plexus forms an efficient anastomosis between the anterior and posterior circulation along the entire length of the spinal cord. Intercostal arteries reach the spine via an anterior and posterior radicular artery. The anterior radicular artery divides into an ascending and descending anterior spinal artery. Therefore, the anterior spinal artery represents an anastomotic channel between ascending and descending branches of neighboring anterior radicular arteries [2]. One should keep in mind that only in few instances do the anterior and posterior radicular

arteries pass the dura to reach the surface of the medulla. Most of the feeding radicular arteries become obliterated during development.

The venous system is divided into intrinsic and extrinsic systems. The intrinsic veins are divided into sulcal and radial veins, and the extrinsic veins consist of the anterior and posterior spinal veins. The anterior median spinal vein follows the anterior spinal artery and continues to the filum terminale vein. One posterior median vein, the greatest spinal vein, is accompanied by two posterolateral veins.

The extrinsic system is in contact with the spinal pia mater and includes the pial venous network, the longitudinal collectors, and the radicular veins. This configuration produces large lateral and dorsoventral anastomotic systems. Spinal veins drain into the anterior and posterior radiculomedullary veins, which in turn drain into the paravertebral and intervertebral plexuses. These venous plexuses drain into the segmental veins, draining into the ascending lumbar veins, azygos system, and pelvic venous plexuses.

5.3 Spinal Cord Ischemia

Spinal cord ischemia accounts for 5–8 % of all acute myelopathies [5] and 1–2 % of all ischemic events within the central nervous system [6].

Pathophysiology

Acute cerebral ischemias are most often caused by either atherosclerotic plaques, cardiac, or arterio-arterial embolism. The situation in the spinal cord is different. Here main causes are pathologies and interventions related to the aorta. Furthermore, infection leading to epidural thrombosis with secondary spinal cord infarction, hypercoagulable state, vasculitis (panarteritis nodosa, antiphospholipid antibody syndrome, systemic lupus erythematosus), epidural transforaminal injections, and cocaine consumption can induce spinal cord ischemia. Degenerative spine disease, for example, a vertebral disk, can directly compress a radicular artery [7]. Alternatively, material from the disk can enter the vascular system and cause so-called fibrocartilage embolism, which has been confirmed histologically. In children and young adults, spinal ischemia following scoliosis surgery has been reported. There it is most likely to be caused by traction movement of the spine. A confirmed cause is surgical occlusion of segmental arteries in the course of scoliosis surgery [8]. Nevertheless, the incidence seems to be low despite frequent occlusion of segmental arteries during respective surgeries. A retrospective study of 1090 patients undergoing corrective spinal deformity surgery reported only four cases with neurological deficits, which were attributed to vascular insufficiency due to vessel ligation [9]. Hyperextension of the thoracic spinal cord has been proposed as a mechanism to cause compression with consecutive occlusion and/or vasospasm and as a result spinal cord infarction in so-called surfer's myelopathy. Quite a number of cases have been reported, typically novice surfers lying and paddling on the board in a supine position for prolonged periods of time [10].

Severe hypotension, cardiac arrest, or, rarely, spinal venous pathology preceding transient ischemic attacks affecting the spinal cord are rare.

Most of spinal cord ischemias are related to therapeutic interventions – either open repair of descending thoracic aortic pathologies or thoracic endovascular aortic repair (TEVAR) – to invasively repair aortic dissection or aneurysm. The incidence of spinal cord ischemia appears to be slightly lower with open repair strategies (between 3 and 15 %), most likely promoted by aortic cross-clamping, reperfusion injury, and acute hemodynamic changes [11]. The incidence of spinal cord following TEVAR varies widely. A recent retrospective monocentric analysis [12] from an established center reports an incidence of spinal cord ischemia following TEVAR as high as 31 % (total of 72 patients). Looking only at cases, where proper peri- and postoperative preventive measures were implemented (maintaining sufficient blood pressure, CSF drainage), the incidence decreased to almost 24 %. In contrast, in a meta-analysis of more than 4000 patients undergoing TEVAR, the rate of spinal cord ischemia was reported as low as 3.9 % [13]. A retrospective analysis of 424 patients undergoing TEVAR revealed a total of 12 patients (2.8 %) suffering from spinal cord ischemia [11]. Onset of ischemia was usually delayed by 10.6 h with a single case showing a paraparesis roughly 10 days after the intervention. The delayed onset of spinal cord ischemia has been attributed to postoperative hypotension, thrombosis, hematoma, embolization, and elevated CSF pressure. Of note, half of the spinal cord ischemia patients had previous open or endovascular aortic repair. As independent risk factors to develop ischemia, chronic renal insufficiency and extent C endovascular coverage (entire descending thoracic aorta from the left subclavian artery to the diaphragm) were identified. Means to raise spinal cord perfusion, before or after symptoms of spinal cord ischemia became apparent (raising arterial blood pressure, lumbar drainage to reduce cerebrospinal fluid pressure), were suggested to ameliorate neurological deficits and to contribute to more substantial recovery in the long term. Surprisingly, 9 out of 12 patients completely recovered from paraparesis (incomplete sensorimotor deficits), whereas 3 out of 12 patient at least incompletely recovered from paraplegia. Only one patient did not recover at all.

Based on the pattern of spinal cord infarction, defined etiologies have been suggested in a case series of 27 spontaneously occurring spinal cord ischemias [14]. Their mean age was 56 years with 11 men and 16 women. They were divided in an anterior, posterior spinal artery pattern, central or transverse manifestations. Concomitant infarction of the vertebral body was observed in one patient. The manifestation typically occurred within minutes up to several hours and was preceded only in two cases by transient ischemic attack (TIA)-like symptoms. Back or neck pain was observed in two thirds of the patients. The authors propose that arterial hypotension causes a central all the way up to a transverse spinal cord lesion pattern. On the other hand, anterior or posterior unilateral or bilateral infarctions are likely caused by mechanical affection of their corresponding vessel – the radicular arteries. This was based on the coincidence of “mechanical factors” referred to as “spine disease.” 75 % of the patients with anterior or posterior infarcts displayed disk pathology (protrusion) coinciding frequently with the infarct region. Respective

mechanical factors can be aggravated by movement of the spine, preceding the occurrence of infarction in a number of patients with anterior/posterior infarction pattern. Of course, fibrocartilage embolism, as described by a number of case reports, and confirmed postmortem histologically cannot be excluded as an underlying mechanism. Overall, recovery in this series of spontaneous spinal cord ischemia cases was remarkably positive with complete or incomplete recovery in 70 % of the patients. In comparison, retrospective studies with spinal cord ischemia patients induced by aortic pathology (with or without surgery) revealed that at least 50 % of the patients showed an unfavorable outcome with permanent wheelchair dependency [5].

Diagnostics

MRI represents the gold standard to visualize ischemic changes. Nevertheless, MRI of the spinal cord can be rather challenging, which is attributed to the need for strong gradients, the small size of the spinal cord, and flow artifacts among others. Axial and sagittal T1-, T2-, STIR-, and diffusion-weighted images are recommended. Contrast enhancement is absent in the initial stage and can therefore help to delineate the pathology from inflammatory or neoplastic causes. Subsequently, contrast enhancement can be observed in the majority of spinal cord ischemia cases – typically more than 2 days after disease onset [15]. In the acute stage, restriction of diffusion and hyperintense signal changes in T2 and STIR sequences can be observed. However, depending also on the quality of the scan, MRI can be without any relevant changes. According to a longitudinal analysis with serial MR scans over time, signal changes in T2-weighted images are typically observed within 2 days from disease onset; the earliest respective change was seen already 14 h after disease onset [15]. Occlusions of the anterior spinal artery can cause predominant infarction of the anterior horn and surrounding white matter uni- or bilaterally, whereas occlusion of the posterolateral artery affects the dorsal horn and the dorsal columns. Concomitant infarction of the vertebral body – associated with hyperintense signal changes in the vertebra and the adjacent disk – is due to the shared vascularization of the spinal cord and the vertebrae [14].

As pointed out above, MRI can be unremarkable in the early phase after spinal cord ischemia. In this case, an infectious/inflammatory cause of spinal cord disease has to be addressed requiring a CSF workup. The general conception is that the CSF in spinal cord ischemia is pretty much normal except for a moderate protein increase. Systematic findings about CSF results in spinal cord ischemia are sparse. In a case series of 13 patients with spontaneous spinal cord ischemia, a mean cell count of 35.4 cells/mm^3 (range 1–160) and a mean protein level of 0.72 g/l (range 0.4–1.39) have been reported [16]. Accordingly, moderate CSF pleocytosis does not rule out spinal cord ischemia entirely.

Therapy

In respect to evidence-based treatment for spontaneously occurring spinal cord ischemia, no randomized controlled clinical studies exist to date. Rule number one

is to identify and treat the underlying cause if possible. Prophylactic treatment with a platelet inhibitory drug such as acetylsalicylic acid is commonly recommended. Thrombolytic treatment with recombinant tissue plasminogen activator (rt-PA) is not established in spinal cord ischemia. Few case reports describe a favorable outcome, which is not sufficient to recommend this therapeutic approach [17, 18]. It is challenging to confirm the diagnosis spinal cord ischemia before the treatment window for rt-PA closes. Due to a missing rationale and evidence, steroids should not be administered.

In respect to treatment and prophylaxis following surgical aortic repair, numerous studies have been performed. It is widely accepted that blood pressure needs to be stabilized immediately. At the same time, spinal cord pressure should be lowered by means of CSF drainage. A meta-analysis investigating 46 studies with a total of 4936 patients, who underwent TEVAR, did not reveal a significant benefit for routine or selective prophylactic lumbar CSF drainage [13]. In contrast, for open aortic repair strategies, the benefit of routine CSF drainage has been confirmed in meta-analyses and a randomized controlled trial [19].

Segmental artery occlusion in the course of anterior spine surgery – mostly related to scoliosis surgery – can induce spinal cord ischemia in rare instances [9]. Preoperative spinal angiography might be useful in determining the exact location of the Adamkiewicz artery and thus allows exact planning of the surgical approach to prevent a lesion of this very important artery. In 100 preoperative angiographies, the Adamkiewicz artery was located between the segments T8 and L3 (in 50 % at the T8/T9 level) and in 75 % on the left side. This information led to ten side changings and three modifications of surgical technique with segmental vessel preservation. In none of the 100 patients, neurological deficits suggesting spinal cord ischemia were observed postoperatively [20].

5.4 Spinal Vascular Malformations

Spinal vascular malformations are divided into spinal dural arteriovenous fistulas (sdAVF), arteriovenous malformations (sAVM), and cavernous angiomas. Both sdAVF and sAVM account for roughly 4 % of all intraspinal lesions.

5.4.1 Spinal Dural Arteriovenous Fistula

Spinal dural arteriovenous fistula (sdAVF) or type I sAVM is the most common type of a spinal vascular malformation accounting for 80 % of all spinal vascular malformations (Fig. 5.3a). The incidence is estimated around 5–10 per one million [21]. Predominantly affected are men with a mean age of 60. It is thought that sdAVF is most likely an acquired disease condition, caused by infection, syringomyelia, trauma, or surgery. 90 % of all sdAVFs are located in the thoracolumbar region [21].

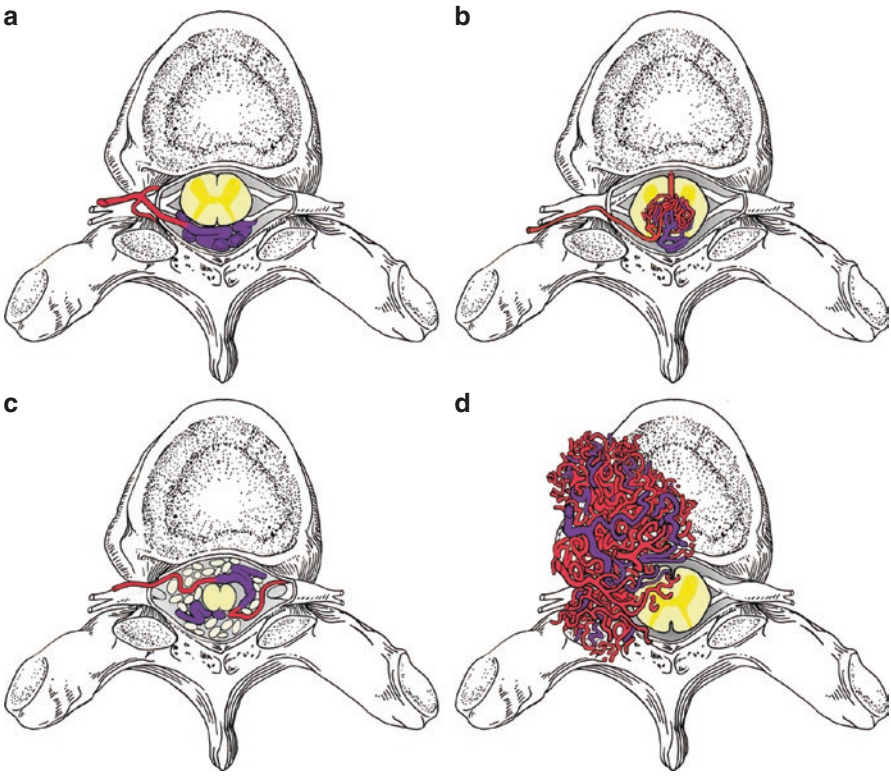

Fig. 5.3 Spinal vascular malformations. (**a**) Spinal dural arteriovenous fistula (sdAVF): typically varicosely expanded veins along the dorsal surface of the spinal cord. (**b**) Spinal arteriovenous malformation (sAVM) type II: Feeders from the anterior and the posterior spinal artery are illustrated. The nidus is located, both intra- and extramedullary. (**c**) The sAVM type IV is located around the conus medullaris on the pial surface intradurally. (**d**) sAVM type III, which do not respect tissue borders, are located intra- and extradurally [26]

Pathophysiology

Root veins penetrate the dura, which contributes to the vessel wall. There, arterial blood is shunted into perimedullar veins causing congestion within the veins and subsequent edema within the spinal cord. Usually solitary, rarely 2, never more than 2 fistulas per patient can be detected. Consecutively, variously expanded veins along the dorsal surface of the spinal cord can be observed. The related venous congestion causes a myelopathy. The fistula is located at the level of the spinal root.

Clinical Presentation

The hallmark of the disease is slowly progressing neurological dysfunction, in particular sensory (superficial and deep sensation) dysfunction and signs of neurogenic bladder and bowel dysfunction [22]. Frequently, at the time of diagnosis, locomotor impairment is observed. The slowly progressing disease course frequently delays the proper diagnosis – on average 23 months from first symptoms until the correct

diagnosis has been made [22]. Sometimes, a stepwise worsening, rarely an acute deterioration, occurs. At disease onset pain – irradiating backache, which may be misinterpreted as degenerative vertebral disease – or claudicatio spinalis are not uncommon. Typically, bed rest provides relief of symptoms, whereas activity aggravates symptoms. If untreated, the disease will result in sensorimotor complete paraplegia including severe bowel and bladder dysfunction.

Diagnostics

Prime diagnostic tool is MRI to detect the congestion myelopathy or perimedullar ectatic veins (flow void in T2-weighted images). Contrast-enhanced MR angiography can help to identify the nidus. More specific analysis of vascular feeders requires conventional angiography. In case MRI is not possible, myelography can be an option to detect enlarged blood vessels in sdAVF, showing enlarged vessels as tortuous filling defects within the subarachnoid contrast dye. MRI shows congestion myelopathy expanding for over 6–7 segments [23]. The rostro-caudal extent of the myelopathy does not correlate with severity of symptoms or location of the fistula [24]. Contrast enhancement may mislead toward a spinal neoplasm. The dilated coronal plexus veins have a nodular, more shaggy appearance, as opposed to less tortuous plexus veins with a more oblong orientation found as a normal variant. Conventional spinal angiography represents the gold standard to identify the exact vascular pathology, in particular the feeding artery and the venous drainage. The disadvantage is that spinal angiography is time-consuming, sometimes requiring more than one session. Ideally, contrast-enhanced MR angiography indicates the fistula site, which helps to save iodinated contrast agent and radiographic exposure time. Alternatively, multislice CT angiography can help to localize the fistula site [25].

In spinal cavernous angiomas, T1-weighted images show hypointense and T2-weighted images hyperintense signal changes. Hemosiderin-sensitive sequences help to clearly identify the cavernous angiomas. Conventional angiography helps to specify an unknown mass lesion or other kinds of vascular pathologies [26].

Therapy

Effective treatment of sdAVF can be achieved surgically or through an endovascular approach. Surgical techniques include hemilaminectomy, identifying the abnormally enlarged shunting radicular vein, and either clipping or coagulating it close to its exit point from the dura. Endovascular embolization uses liquid adhesive embolic agents to interrupt the intradural shunting vein. The endovascular approach is minimally invasive, and the treatment of the fistula can often be performed in combination with the diagnostic procedure. The length of hospitalization is usually shorter [27]. Nevertheless, the overall outcome is not affected by the chosen treatment modality [28]. In particular motor symptoms and pain respond, rarely bowel and bladder dysfunction. However, a recent meta-analysis shows a clear advantage of primary surgical treatment of sdAVF over endovascular treatment in terms of initial fistula closure

and fistula recurrence [29]. Successful treatment (lack of initial treatment failure and lack of recurrence) can be achieved in 96.6 % (588 out of 609 patients) with surgery versus 72.2 % (363 out of 503 patients) with endovascular therapy.

5.4.2 Spinal Arteriovenous Malformations

Spinal arteriovenous malformations (sAVM), which are mostly located at cervical spinal cord level, account for 15–20 % of all spinal vascular malformations. The average age in type II sAVM is 20–40 years. Type III and IV sAVM become apparent in adolescence and early adulthood (Fig. 5.3b–d).

Pathophysiology
In type II sAVM, multiple arterial feeders take their origin from anterior and posterior spinal arteries. Therefore, arterial pressure is usually high. Drainage occurs through the venous plexus. The nidus is mostly confined to a spinal cord segment sitting partly intra- and partly extramedullary. An intramedullary or subarachnoidal hemorrhage or a venous congestion leads to mostly acute clinical symptoms. Type III sAVM is characterized by a diffuse nidus enlarging the spinal cord. Clinical symptoms are triggered by hemorrhage or myelopathy related to the venous congestion. Type IV sAVM is located around the conus medullaris on the pial surface intradurally. As described for type III sAVM, the malformation becomes apparent by hemorrhage or venous congestion with subsequent myelopathy or radiculopathy.

Diagnostics
See respective paragraph for spinal dural arteriovenous fistula.

Therapy
In type II sAVM, decompression surgery alone (laminectomy) does not yield a favorable outcome. Surgical and endovascular therapeutic interventions can be considered to remove/extinguish the sAVM. However, outcome appears to be more favorable with endovascular therapy requiring in many cases repeated interventions [26]. Without specific treatment the overall prognosis is poor. Type III sAVMs can rarely be resected, whereas in type IV sAVM, successful surgical resection is feasible [26].

5.4.3 Spinal Cavernous Angioma

Spinal cavernous angiomas represent rare disease conditions, which manifest around the age of 40. Compared to intraspinal locations, intracranial cavernous angiomas are ten times more frequent [26].

Pathophysiology
Cavernous angiomas consist of telangiectasias, which change in shape and size through repeated bleedings. They can be located within or outside of the spinal cord parenchyma, rarely, epidurally.

Clinical Presentation
Back pain and progressive neurological symptoms (intraparenchymal angioma) are caused by repeated bleeding and/or microthrombosis. In case of a slowly progressive disease course, the diagnosis can be delayed up to 4 years. If symptoms manifest acutely, the diagnosis will be established promptly.

Diagnostics
See respective paragraph for spinal dural arteriovenous fistula.

Therapy
The main aim should be to surgically remove symptomatic cavernous angiomas; however, the perioperative risk has to be weighed carefully against disease progression [30].

Conclusion

Spinal cord vascular pathologies can present as acute onset (spinal cord ischemia) all the way to a chronically progressive disease course. Clinical symptoms are not specific in respect to the etiology. In particular slowly progressing symptoms as typically observed in sdAVM can dramatically delay the proper diagnosis and thus postpone specific treatment. The sooner appropriate measures are taken – endovascular or surgical elimination of the fistula – the earlier neurological dysfunction can be contained, and further worsening including bowel and bladder dysfunction can be avoided. In spinal cord ischemia, early diagnosis can be challenging despite the acute presentation of severe neurological dysfunction and not infrequently made just by exclusion of other compressive and non-compressive causes of spinal cord disease. Unfortunately, effective therapeutic interventions (systemic administration of recombinant tissue plasminogen activator, mechanical thrombus retrieval), which are available after acute cerebral ischemia, are not established in spinal cord ischemia.

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Infectious, Autoimmune and Other Immune-Mediated Causes of Myelitis

6

Ingo Kleiter, Erich Schmutzhard, and Corinna Trebst

Abstract

Autoimmunity, infections and immune-mediated mechanisms associated with pathogens, vaccinations and systemic diseases can damage the spinal cord and its adjacent structures. Multiple sclerosis is the most common cause of autoimmune myelitis, preferably affects young women and takes a relapsing–remitting or progressive course. In children, acute disseminated encephalomyelitis frequently accounts for acute myelitis. The clinical hallmarks of neuromyelitis optica spectrum disorder are recurrent episodes of optic neuritis and longitudinally extensive transverse myelitis. Further immune-mediated causes of myelitis include sarcoidosis, Sjögren's disease, spinal manifestations of systemic autoimmune and inflammatory diseases as well as paraneoplastic, para-/postinfectious and para-/post-vaccinal aetiologies. Diagnostic criteria rely on clinical and magnetic resonance imaging features together with serum and cerebrospinal fluid examination.

Infections with viruses, bacteria, spirochaetales, fungi, protozoa or helminths can affect the spinal cord, nerve roots and adjacent structures, frequently resulting in severe long-term sequelae. Herpes virus transverse myelitis and the tick-transmitted diseases neuroborreliosis and tick-borne encephalitis are the most common causes of infectious myelitis in Central Europe, whereas on a worldwide scale, myelitis caused by enteroviridae (e.g. poliomyelitis or enterovirus) and spinal neurocysticercosis are more frequent. The diagnosis of

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infectious spinal cord disease is made by cerebrospinal fluid analysis with elevated cell counts and detection of pathogens by microscopy or polymerase chain reaction or a specific intrathecal antibody reaction. Since infectious and autoimmune myelitis are associated with significant morbidity and mortality and often account for severe neurological deficits as well as long-term sequelae, early and specialised multidisciplinary care are recommended.

6.1 Immune-Mediated Myelitis

6.1.1 Introduction

Autoimmune and other immune-mediated causes of myelitis are common and often occur in the context of a more widespread inflammation involving the brain or other organs. Isolated spinal manifestations, particularly idiopathic transverse myelitis and longitudinally extensive transverse myelitis, may occur. The worldwide incidence of acute transverse myelitis is projected to be between 1.35 and 4.6 per million per year [10].

Multiple sclerosis is the most common cause of autoimmune myelitis in adults, whereas acute disseminated encephalomyelitis frequently accounts for acute myelitis in children. Further immune-mediated causes of myelitis include neuromyelitis optica spectrum disorder, sarcoidosis, Sjögren's disease, spinal manifestations of systemic autoimmune and inflammatory diseases as well as paraneoplastic, para-/postinfectious and para-/post-vaccinal aetiologies (Table 6.1).

The clinical features of autoimmune and immune-mediated myelitis are mainly defined by the anatomic location and extent of injury to the spinal cord in its craniocaudal and transverse axes, to a lesser degree by the immune mechanisms involved. Apart from Sjögren's syndrome and para-/postinfectious, paraneoplastic and para-/post-vaccinal aetiologies, which can all present with concomitant radiculitis and cause flaccid paresis, weakness is usually of the upper motor neuron type with associated spasticity, exaggerated reflexes and extensor plantar reflexes.

6.1.2 Multiple Sclerosis

Multiple sclerosis (MS) is the most common autoimmune demyelinating disease of the central nervous system (CNS), showing a female preponderance [35]. MS can take a relapsing–remitting or a primary or secondary progressive disease course, the latter with or without active inflammation [111]. A primary manifestation or relapses of MS as myelitis is common and is the most frequent cause of autoimmune myelitis. In individuals with known MS, a new spinal manifestation should therefore primarily be diagnosed and treated as an MS relapse. Spinal cord lesions in MS are typically short, spanning over one or two segments, and localised laterally in the spinal cord (Fig. 6.1). Contrast enhancement is seen regularly in acute lesions. A longitudinal

Table 6.1 Autoimmune and immune-mediated myelitis: Clinical presentation and diagnostic characteristics

Disease[a]	Clinical presentation and diagnostic characteristics
Myelitis with autoimmune-/immune-mediated CNS disorders	
Multiple sclerosis (MS)	Relapsing or progressive, lesions typically short and laterally localised in the spinal cord, cranial MRI with signs of dissemination in time and space, typical CSF findings (pleocytosis, oligoclonal bands, intrathecal IgG production)
Neuromyelitis optica spectrum disorder (NMOSD)	Relapsing, lesions typically presenting as longitudinal extensive transverse myelitis (LETM) spanning over ≥3 vertebral segments, often centrally located, cranial MRI not typical for MS, serum anti-aquaporin-4 antibodies
Acute disseminated encephalomyelitis (ADEM)	Monophasic (multiphasic possible), associated with previous infections and vaccination, MRI with large lesions in the cerebral white and grey matter, often of the same age and gadolinium enhancing, no dissemination in time, CSF without oligoclonal bands
Idiopathic transverse myelitis	Monophasic, CSF pleocytosis, positive oligoclonal bands (often transient)
Paraneoplastic	Association with solid tumours or haematological neoplasms, often paraneoplastic antibodies
Para-/postinfectious	Monophasic, associated with previous infection, often brain involvement
Para-/post-vaccinal	Monophasic, associated with previous vaccination, can be accompanied by radiculitis and inflammatory polyneuropathy
Anti-TNFα agents	Association with anti-TNFα therapy for rheumatoid arthritis, demyelinating, can additionally affect brain and peripheral nervous system
Myelitis as complication of inflammatory multisystem disorders	
Sarcoidosis	Often LETM, brain and cranial nerve involvement possible, pulmonary or lymph node manifestations (not always), soluble IL-2 receptor elevated in serum, definite diagnosis by biopsy
Sjögren's syndrome	Dry eyes and reduced production of saliva (sicca syndrome), anti-SS-A antibodies, anti-SS-B antibodies
Systemic lupus erythematosus (SLE)	Neuropsychiatric complications, anti-nuclear antibodies (ANA), anti-double-stranded DNA (anti-dsDNA) antibodies, antiphospholipid antibodies
Behçet's disease	Recurring aphthous stomatitis, genital ulceration, uveitis and arthropathy
Mixed connective tissue disease (MCTD)	Rare, often affecting thoracic cord
Systemic sclerosis	Rare, transverse myelopathy
Vasculitis	Rare, necrotising myelopathy

[a]Order from highest to lowest prevalence

myelitis is not typical for MS and should trigger alternative diagnoses such as neuromyelitis optica spectrum disorder (NMOSD, see below). Patients presenting with a monofocal myelitis and asymptomatic brain lesions without contrast enhancement have a high risk of developing a clinically definite MS in the future [138]. With at

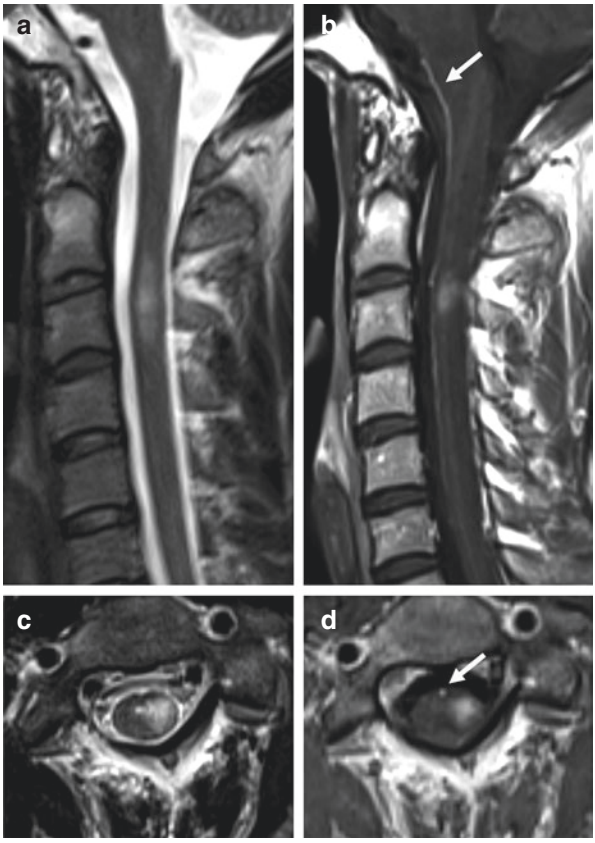

Fig. 6.1 Multiple sclerosis (MS). Spinal MRI of a 23-year-old male presenting with subacute onset of right-sided hypaesthesia of the trunk. The patient was subsequently diagnosed with a relapsing–remitting MS. (**a**, **b**) Sagittal and (**c**, **d**) axial T2- and T1-weighted images show a monosegmental laterally located myelitis. (**b**, **d**) Gadolinium enhancement is shown. *Arrows* indicate the anterior spinal artery (Images courtesy of Dr. Peter Raab, Neuroradiology, Hannover Medical School)

least two additional lesions in cranial MRI, one with contrast enhancement, the current diagnostic criteria allow the definite diagnosis of MS [141] and underline the importance of a cranial MRI in patients initially presenting with a clinically isolated myelitis. CSF examination reveals a mild pleocytosis, normally below 50 cells/μL with a predominance for activated lymphocytes. Oligoclonal bands and signs for a polyspecific intrathecal antibody production are found in the majority of MS patients and support the diagnosis. A thorough differential diagnosis should exclude other causes. Treatment of spinal manifestation of MS follows the general recommendations of relapse treatment including high-dose steroids and in the case of steroid-refractory functional deficits the use of apheresis therapies (see Sect. 6.1.11). Long-term treatment of MS is based on the use of immunomodulatory and immunosuppressive strategies.

6.1.3 Neuromyelitis Optica Spectrum Disorder

Neuromyelitis optica spectrum disorder (NMOSD) is a disabling autoimmune condition of the CNS characterised by inflammation predominantly of the optic nerves and the spinal cord. Neuromyelitis optica (NMO), also known as Devic's disease, was long considered a variant of MS. However, the discovery of highly specific serum autoantibodies against aquaporin 4 (AQP4) in a subset (60–80 %) of patients with NMO has identified NMO as a distinct disease entity completely separate from MS [12, 22, 108, 196]. With characterisation of patients with AQP4 antibodies but not the full clinical picture of NMO, the spectrum of the disease entity has been expanded, and the term NMO spectrum disorder (NMOSD) was introduced [197]. In 2015, the diagnostic criteria of NMOSD were revised and underline the importance of the presence of AQP4 antibodies with stratifying NMOSD in those with and without AQP4 antibodies [198]. The core clinical characteristics required for patients with NMOSD with AQP4 antibodies include clinical syndromes or MRI findings related to optic nerve, spinal cord, area postrema and other brainstem, diencephalic or cerebral presentations. More stringent clinical criteria, with additional neuroimaging findings, are required for diagnosis of NMOSD without AQP4 antibodies or when serologic testing is unavailable.

Spinal cord affection in NMOSD patients shows typically an LETM, which is defined as spanning over at least three vertebral segments (Fig. 6.2). Lesions are often found centrally in the spinal cord. Contrast enhancement is patchy and long lasting. Recently, anti-MOG antibodies were detected in some AQP4 antibody-negative NMOSD patients, constituting approximately 5 % of all NMOSD patients [102, 112, 155]. NMOSD has a strong female preponderance (up to 10:1 depending on geographical region). The occurrence and frequency of myelitis in the first year predicts the long-term course of NMOSD [86]. Contrary to MS, myelitis in NMOSD often leaves residual deficits with complete remissions in only 20 % of cases. Since the outcome of NMOSD attacks is decisive for long-term disability, early escalation of attack treatment is recommended [103]. Apheresis therapies might be superior to high-dose corticosteroids for the first-line treatment of NMOSD myelitis [103]. Concomitant autoimmune or rheumatologic diseases occur in up to 40 % of patients with NMOSD [82]. LETM can also be found of other origin than in NMOSD; therefore, a thorough differential work-up is essential [186]. Long-term treatment of NMOSD is immunosuppressive; first-line therapies are azathioprine or rituximab [187].

6.1.4 Acute Disseminated Encephalomyelitis

Acute disseminated encephalomyelitis (ADEM) is a monophasic (multiphasic possible) inflammatory multifocal disease of the CNS [180]. ADEM typically affects children and young adults. An association with previous infections and vaccination has repeatedly been reported [149]. Clinical presentation ranges from a prodromal phase with fever, headache and nausea to the rapid appearance of multifocal

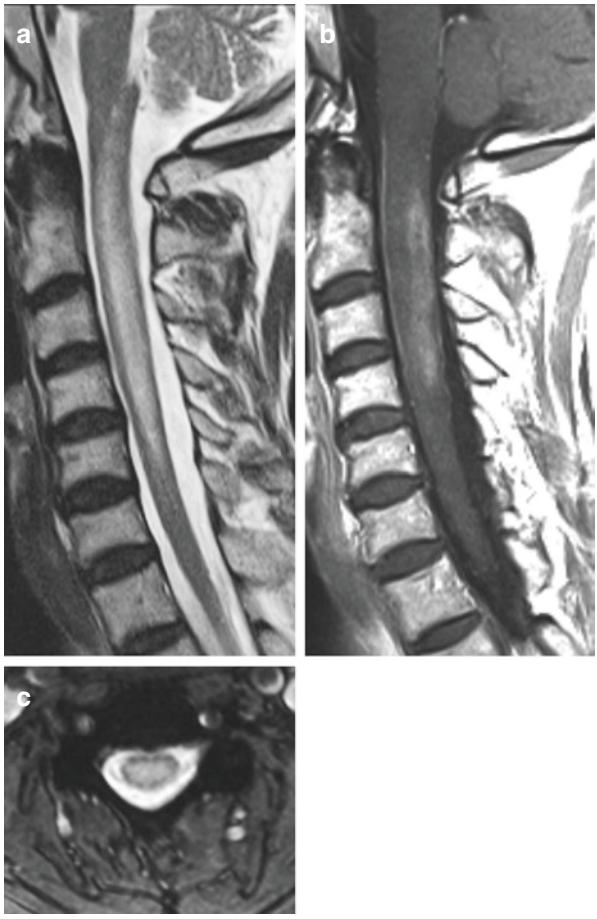

Fig. 6.2 Neuromyelitis optica spectrum disorder (NMOSD). Spinal MRI of a 61-year-old woman with acute painful tetraparesis and aquaporin-4 antibody-positive NMOSD. (**a**) Sagittal T2-weighted and (**b**) axial T2-weighted images show a longitudinally extensive transverse myelitis (LETM) spanning five vertebral segments and the whole axial plane. Notice spinal oedema with swelling of the myelon. (**c**) Patchy, "cloud-like" gadolinium enhancement on T1-weighted sagittal image (Images courtesy of Prof. Carsten Lukas, Radiology, St. Josef Hospital Bochum)

neurological deficits, often accompanied by reduced consciousness and a psychosyndrome. Cranial MRI typically exhibits large lesions in the white and grey matter with perifocal oedema, often of the same age and gadolinium enhancing [203]. The involvement of the spinal cord is frequently observed, showing lesions of longitudinal extent [9]. ADEM is associated with occurrence of anti-MOG antibodies, particularly in children [11, 112].

Diagnosis is based on the combination of clinical presentation, cranial MRI with multifocal lesions of the same age, spinal MRI with longitudinal myelitis and CSF examination revealing mild to moderate pleocytosis and absence of

oligoclonal bands. Therapy comprises of high-dose methylprednisolone but can also include therapeutic plasma exchange, intravenous immunoglobulins and immunosuppressants.

6.1.5 Idiopathic Transverse Myelitis

The diagnosis of an idiopathic transverse myelitis (ITM) is based on exclusion of other diseases. About 40 % of acute transverse myelopathies remain unexplained [163]. The "Transverse Myelitis Consortium Working Group" (TMCWG) has proposed diagnostic criteria for an idiopathic transverse myelitis [184]. Besides a typical clinical presentation for a spinal cord lesion, the diagnosis requires signs of an inflammatory aetiology either by MRI (hyperintensities in T2-weighted images, contrast enhancement) or in the CSF with a pleocytosis or intrathecal immunoglobulin production (elevated IgG index). Other aetiologies, particularly infectious or autoimmune disease, vascular or metabolic disease and hypovitaminosis, have to be excluded by a thorough differential diagnostic work-up.

ITM usually is monophasic and has a good outcome in the majority of patients [184]. About one third of patients initially diagnosed with an ITM and normal cranial MRI will develop a clinically definite MS within 5 years [138]. Recurring transverse myelitis without other CNS manifestation can occur in about 8 % of patients with an acute isolated ITM [166].

6.1.6 Myelitis with Systemic Autoimmune Diseases

Spinal cord affliction can occur as a complication of multisystem autoimmune or inflammatory disorders, for example, sarcoidosis, Sjögren's disease, systemic lupus erythematosus (SLE), Behçet's disease, mixed connective tissue disease, vasculitis and others.

6.1.6.1 Sarcoidosis

Sarcoidosis is a granulomatous disease of unknown aetiology which typically involves various organs with a predilection of the lungs (in about 90 % of patients) and lymph nodes [38, 89]. Clinical involvement of the CNS usually occurs early in the disease and is reported in approximately 5–15 % of cases [175]. Cranial neuropathy, papilloedema, aseptic meningitis, hydrocephalus, seizures, psychiatric symptoms, cerebral and also spinal lesions as well as peripheral neuropathy and skeletal muscle involvement have been described as neurological complications. Spinal lesions are typically longitudinally and centrally located in the cord (Fig. 6.3). Primary manifestation of a sarcoidosis as an LETM in the nervous system is possible [19]. Diagnostic work-up includes CSF analysis showing mild to moderate pleocytosis and mild disruption of the blood–brain barrier, serum soluble IL-2 receptor, chest imaging and whole body FDG-PET scan to identify hypermetabolic lymph nodes. Definite diagnosis of sarcoidosis still has to be

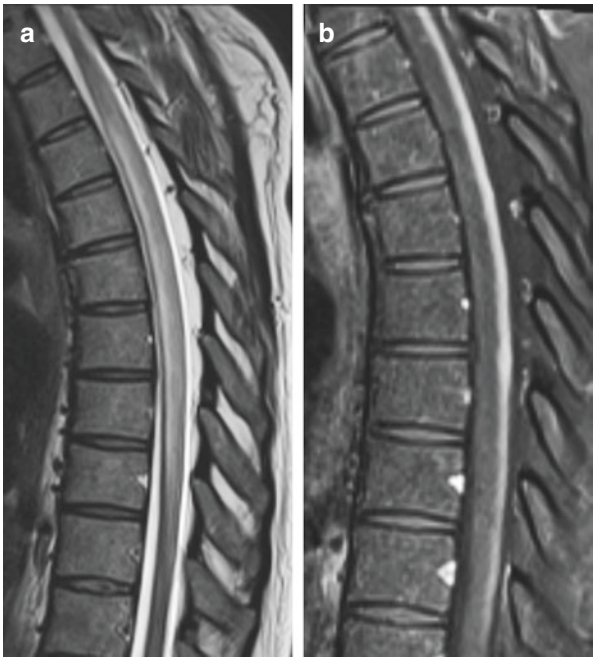

Fig. 6.3 Neurosarcoidosis. MRI of the thoracic spinal cord of a 52-year-old woman with acute paraparesis and biopsy-proven pulmonary sarcoidosis. (**a**) Sagittal T2- and (**b**) fat-suppressed T1-weighted images after gadolinium injection show a longitudinally extensive lesion with enhancement of the dorsal column (Images courtesy of Prof. Carsten Lukas, Radiology, St. Josef Hospital Bochum)

inferred from biopsy. Therapy comprises of corticosteroids and immunosuppressants; in rapid progressive cases, successful treatment with infliximab has been reported [30, 88, 192].

6.1.6.2 Sjögren's Syndrome

Sjögren's syndrome is a systemic autoimmune disease that affects primarily the exocrine glands and is associated with anti-SSA (anti-Ro) and anti-SSB (anti-La) antibodies [194]. Typical symptoms are dry eyes and reduced production of saliva. Vasculitis and CNS involvement can be observed as typical and frequent extraglandular manifestations of primary Sjögren's syndrome [48, 60]. A painful, mostly sensory polyneuropathy and sensory ganglionopathy are the most frequent neurological complications. CNS involvement shows a wide spectrum, occurs far less often and includes asymptomatic white matter lesions on MRI but also severe focal neurological symptoms including optic neuritis and transverse myelitis [48]. Myelitis often is longitudinal in extent and can affect all parts of the cord [14]. Overlap syndromes with NMOSD are frequently encountered; hence, testing for AQP4 antibodies is recommended [14, 85].

6.1.6.3 Systemic Lupus Erythematosus (SLE)

Neurological involvement in patients with SLE is frequent and ranges from mild neurocognitive dysfunction and mood changes to severe psychiatric and neurological manifestations such as seizures, stroke and psychosis [15]. Spinal cord involvement is less common (about 1–2 %) and mostly presents as transverse myelitis [105]. Myelitis with longitudinal extent has also been reported [76, 125]. Diagnostic work-up should include serological tests in search for anti-nuclear antibodies (ANA), anti-double-stranded DNA (anti-dsDNA) antibodies and antiphospholipid antibodies. CSF analysis shows mild to moderate pleocytosis and mild disruption of the blood–brain barrier. Severity of neurological impairment during myelitis is a prognostic marker for long-term outcome [154]. Overlap syndromes with NMOSD are reported [154] and testing for AQP4 antibodies is recommended [85].

6.1.6.4 Behçet's Disease

Behçet's disease as another chronic, multisystem, inflammatory disorder is characterised by a small vessel vasculitis [24]. The clinical picture is dominated by recurring aphthous stomatitis, genital ulceration, uveitis and arthropathy [40]. Neurological manifestations commonly involve the basal ganglia and brainstem and occur in up to a third of the patients [2]. In approximately 10 % of Behçet cases with neurological manifestation, spinal cord involvement is reported. LETM can also be the sole presentation of neuro-Behçet's disease [39]. Myelitis associated with Behçet's disease often presents as longitudinally extensive [58, 190, 201]. Outcome of Behçet-associated myelitis is often poor. Early and aggressive immunosuppressive treatment is critical [98].

6.1.6.5 Mixed Connective Tissue Disease

Spinal cord affection in conjunction with mixed connective tissue (MCTD) disease is extremely rare, has only been reported in single case studies and often presents as transverse myelitis in the thoracic cord [16]. Neurological complications occur in about 10 % of patients with MCTD and are most commonly peripheral neuropathies, meningitis, psychosis and convulsions [126].

6.1.6.6 Systemic Sclerosis

Only few cases of myelitis associated with systemic sclerosis have been reported [110, 182]. Neurological complications of systemic sclerosis are uncommon and usually present as myopathy or neuropathy of cranial or peripheral nerves. Rarely, the CNS or spinal cord is afflicted, the latter as compressive (secondary to osteolysis, calcific deposits or facet arthropathy) or non-compressive transverse myelopathy [6, 110]. MRI, CSF and clinical evaluation support the diagnosis of myelitis, and immunosuppressive therapies are used for remission induction.

6.1.6.7 Vasculitis

The clinical presentation of spinal cord disease associated with vasculitis can range from mild myelitis to severe necrotising myelopathy. Most common causes are

SLE, Behçet's disease and Sjögren's syndrome (see above). Single cases of myelitis in patients with pANCA-associated vasculitis [71], urticarial vasculitis [20] and immune-complex allergic vasculitis [129] have been described. In one 65-year-old man with systemic pANCA-associated vasculitis, MRI showed patchy cord enhancement from T10 to the conus, remitting after steroid therapy [71]. Usually pANCA-positive Wegener's granulomatosis only affects the brain, meninges and cranial nerves.

6.1.6.8 Antiphospholipid Syndrome

The antiphospholipid syndrome (APS) is a systemic autoimmune disorder characterised by presence of antiphospholipid antibodies, recurrent thrombosis and obstetrical morbidity. Neurological manifestations of APS are mainly thrombotic and include stroke, transient ischaemic attack, Sneddon's syndrome, neuropsychological deficits and peripheral neuropathy [146]. In a systemic review covering the literature from 1966 to 2010, 14 cases of APS and simultaneous transverse myelitis were identified [147]. The causal relationship is unclear, particularly since a comorbidity of APS and NMOSD was reported [82, 121] and the presented cases remained untested for AQP4 antibodies.

6.1.7 Paraneoplastic Myelopathies

Myelopathies occurring in association with cancer are rare. Spinal cord paraneoplastic syndromes include inflammatory, necrotising or demyelinating myelitis, which may have a focal, transverse or longitudinally extensive dissemination [42]. Myelitis can be accompanied by motor neuron disease, subacute motor neuronopathy or stiff-person syndrome.

The diagnosis of a paraneoplastic myelitis is made by exclusion of other autoimmune or infectious causes of myelitis and CSF or imaging findings supporting acute inflammation, i.e. CSF pleocytosis and IgG index elevation, as well as gadolinium enhancement. Cancers and paraneoplastic antibodies commonly associated with myelitis include small cell lung carcinoma (anti-Hu, anti-Ri, anti-amphiphysin, anti-CRMP5/CV2, anti-GAD, P/Q and N type calcium channel antibodies), breast carcinoma (anti-PCA1, anti-amphiphysin) and ovarian cancer (anti-Ri) [84, 120]. Additionally, AQP4 antibodies are sometimes found positive, particularly in patients with breast carcinoma and in the elderly [130, 140]. Hence, LETM in the context of NMOSD can also represent a cancer-associated aetiology. Other cancers associated with AQP4 antibodies include lung, thymic and cervical carcinomas, leiomyosarcoma and lymphomas. Apart from cancers, demyelinating myelopathy was also described as a rare manifestation of graft-versus-host disease [63]. The paraneoplastic form of stiff-person syndrome occurs in 5–10 % of patients; is characterised by rapidly evolving pain, rigidity and stiffness; and is frequently associated with anti-amphiphysin, anti-GAD65 or anti-glycine receptor antibodies.

Paraneoplastic myelitis is often progressive and may lead to wheelchair dependency and death [57]. Acute paraneoplastic myelitis is treated with high-dose

corticosteroids, intravenous immunoglobulins and therapeutic plasma exchange and stiff-person syndrome additionally with antispasticity drugs. Therapy of the underlying tumour is the most important long-term treatment; however, since relapses and progressive courses occur, additional immunosuppressive treatment is often needed.

6.1.8 Para-/Postinfectious Myelitis

Myelitis can be associated with concomitant or antecedent viral, rarely bacterial, infections [149]. Patients typically report an upper respiratory tract infection or a nonspecific febrile illness. Para-/postinfectious myelitis may present as isolated, mostly transverse myelitis, or together with a more widespread encephalomyelitis and can range from mild urinary symptoms from a conus/epiconus lesion [143] to severe ADEM and even involvement of the whole peripheral and central nervous system ("encephalomyeloradiculopathy") [114]. An immune-mediated mechanism, i.e. bystander activation or molecular mimicry, is thought to be the pathogenic mechanism. Specific causes of para-/postinfectious myelitis are discussed under the individual pathogens involved. Typical are herpes viruses, orthomyxo- and paramyxoviruses (influenza, measles, mumps) and rubella virus. As with idiopathic transverse myelitis, diagnosis depends on spinal MRI, typically showing gadolinium enhancement and an inflammatory CSF with pleocytosis, abnormal IgG index and sometimes oligoclonal bands but absent pathogen or specific antibody index. Steroid pulse therapy and plasma exchange are used for remission induction, intravenous immunoglobulins in cases with contraindications for these therapies [172]. Since para-/postinfectious myelitis usually is monophasic, long-term immunosuppressive therapy is rarely needed.

6.1.9 Myelitis After Vaccination and as Complication of Immunotherapy

Neurological complications of vaccinations are rare [123]. LETM with local oedema and axonal motor neuropathy was described in a 77-year-old Japanese woman after vaccination against A/H1N1 influenza [156]. In a systematic review of PubMed, EMBASE and DynaMed, 37 cases of transverse myelitis associated with previous vaccinations were found for a period from 1970 to 2009 [1]. Cases were associated with vaccines against hepatitis B, measles–mumps–rubella, diphtheria–tetanus, rabies, poliovirus, influenza, typhus, pertussis and Japanese B encephalitis in decreasing order and typically occurred in the first month after vaccination.

Therapeutic inhibition of the tumour necrosis factor (TNF)-α is associated with CNS demyelination [46, 202]. In a review of 33 patients with neurological complaints which occurred within a median of 10 months after initiation of anti-TNFα agents, 22 had CNS involvement, 16 with encephalitic lesions, 5 with optic neuritis and 8 with transverse myelitis [169]. CSF and evoked potentials frequently are

abnormal in patients with CNS involvement. Myelitis associated with anti-TNFα agents usually is monophasic, but relapsing episodes with final diagnosis of multiple sclerosis have been described. Consequently, anti-TNFα therapy should be discontinued when demyelinating myelitis occurs.

Both myelitis after vaccination and as complication of immunotherapy lack specific clinical and ancillary findings. It is discussed controversially whether the temporal association of vaccinations and anti-TNFα therapies with myelitis indicates a causal relationship, triggering of an underlying disease process, or occurs merely by chance.

6.1.10 Diagnostic Work-Up

Patients presenting with signs and symptoms of acute autoimmune or immune-mediated spinal cord affection should be immediately subjected to MRI of the complete spinal axis. First priority is to rule out a compressive aetiology [184]. The appearance and longitudinal extension of intramedullary lesions can guide diagnosis (Table 6.2). Further diagnostic testing (Table 6.3) should include CSF analysis, blood testing and cranial MRI, since most of these diseases can affect the brain as well [162]. A CSF pleocytosis with a cell count over 50 cells/μl should prompt the consideration of an infectious cause (see below), even though a high CSF cell count does not exclude an autoimmune inflammatory aetiology, particularly NMOSD, or even a neoplastic disorder. Additional blood testing aims to find systemic disorders such as SLE, Sjögren's syndrome or sarcoidosis. A neurological involvement of these disorders should be considered in the setting of a positive serology and typical clinical presentation. The presence of a paraneoplastic antibody should prompt the search for the primary tumour using appropriate imaging techniques and a whole body FDG-PET scan where available. FDG-PET scanning can also be helpful to detect inflammatory lymph nodes in the setting of systemic sarcoidosis.

6.1.11 Therapeutic Strategies

With the exception of MS where additionally immunomodulatory therapies are used, treatment of spinal cord manifestations of autoimmune disorders is immunosuppressive. For acute attacks, high-dose methylprednisolone pulses are first line, sometimes to be followed by therapeutic plasma exchange, immunoadsorption or intravenous immunoglobulins (Table 6.4). When no complete recovery is achieved, immunosuppressive therapy, e.g. with rituximab, cyclophosphamide or mitoxantrone may be used for further remission induction. In the majority of autoimmune spinal cord diseases, the risk of a relapsing course is given; therefore, long-term treatment is required.

Table 6.2 Differential diagnosis of monosegmental versus longitudinal autoimmune myelitis

Lesions typically <3 vertebral segments	Lesions typically ≥3 vertebral segments (LETM)
Multiple sclerosis	NMOSD
ITM	ADEM
Post-vaccinal myelitis	Paraneoplastic myelitis
Para-/postinfectious myelitis	Sarcoidosis
SLE	Behçet's disease

Table 6.3 Diagnostic work-up for autoimmune myelitis

Imaging	CSF analysis	Blood works
Spinal MRI: Sagittal T2-TSE Sagittal pre-/post-contrast T1 (slice thickness of 3 mm) Axial T2-TSE Axial post-contrast T1 (slice thickness of 4 mm or less)	Cell count and differentiation (lymphocyte, granulocyte, erythrocyte), cell cytology, protein, lactate, albumin quotient, immunoglobulin G/A/M quotient, antibody index for measles, rubella, varicella (MRZ reaction), oligoclonal IgG bands	Differential blood count, liver enzymes, serum creatinine, glomerular filtration rate, glucose, rheumatoid factor, anti-nuclear antibodies, ENA screening, anti-ds-DNA antibodies, c/pANCA, antiphospholipid antibodies, soluble IL-2 receptor, vitamin B12
Cranial MRI: Axial T2-TSE/T2-FSE Axial FLAIR Axial T1-SE pre-/post-contrast and coronal T1w post-contrast Sagittal T2-TSE/T2-FSE (3 mm slice thickness), centred medially	*Optional*: Infectious agent screening	*Optional*: AQP4 antibodies MOG antibodies Paraneoplastic antibodies Serology for infectious agents

Table 6.4 Common therapies for acute autoimmune myelitis

Therapy	Regimen	Route	Comments
Methylprednisolone	1 g for 3–5 days	IV	Rescue therapy with 3–5 × 2 g; oral tapering may be needed; regular pulses can be used for interval therapy
Plasma exchange	5–7 exchanges every other day	IV (central line)	Complications related to central line and plasma substitutes
Immunoadsorption	5–7 exchanges every other day	IV (central line)	Specific removal of plasma IgG, complications related to central line
Intravenous immunoglobulins (IVIG)	0.4 g/kg for 5 days	IV	Regular infusions can be used for interval therapy

6.2 Myelitis Caused by Pathogens

6.2.1 Introduction

Infections with viruses, bacteria, spirochaetales, fungi, protozoa or helminths can affect the spinal cord, nerve roots and adjacent structures, frequently resulting in severe long-term sequelae [13]. Herpes virus transverse myelitis and the tick-transmitted diseases neuroborreliosis and tick-borne encephalitis are the most common causes of infectious myelitis in Central Europe, whereas worldwide myelitis caused by enteroviridae (e.g. poliomyelitis or enterovirus) and spinal neurocysticercosis are more frequent. While most pathogens can cause acute myelitis, which represents a medical emergency, chronic myelitis or myelopathy with symptoms evolving over weeks or months is mostly restricted to retroviruses. Table 6.5 summarises the most common pathogens causing myelitis and their endemic regions.

6.2.2 Herpes Family Viruses

Members of the herpes family viruses are capable of invading the CNS and infect particularly neurons. They establish a latent and life-long persisting infection in the dorsal root ganglia (review in [174]). These viruses can cause myelitis by primary infection and/or reactivation and probable spread to the spinal cord [81].

6.2.2.1 Herpes Simplex Virus

Herpes simplex virus (HSV) type 1 is the most common cause of infectious myelitis. HSV-1 myelitis can be subacute or chronic and mostly presents as monosegmental myelitis. Predisposing factors are diabetes mellitus, malignancies and conditions compromising the immune system, for example, immunosuppressive therapy or HIV infection. Nevertheless, not always an underlying condition can be found in individuals with herpes myelitis. Diagnostic work-up should particularly involve analysis of cerebrospinal fluid, normally exhibiting a mild pleocytosis (between 10 and 200 cells/μL) and mild disruption of the blood–brain barrier. Detection of viral DNA by polymerase chain reaction (PCR) in the CSF is the most important diagnostic step and helps to identify the causative agent. Importantly, PCR analysis can be negative for the first days after reactivation/infection. Therefore, the repeated analysis of the humoral immune response in the CSF can be helpful. The appearance of a positive CSF/serum antigen-specific index (ASI) is projected after 7 days of infection. Therapy includes high-dose aciclovir (10 mg/kg body weight IV, three times a day) for at least 14 days. Outcomes are variable; complete recovery is possible. Reoccurrence has been reported in up to 20 % of cases [31].

Table 6.5 Pathogens causing myelitis and their endemic regions

Pathogen	Endemic region
Viruses	
Herpes family viruses (herpes simplex virus, varicella zoster virus, cytomegalovirus, Epstein–Barr virus, human herpes viruses 6 and 7)	Worldwide
Flaviviruses (dengue virus, West Nile virus, tick-borne encephalitis virus, Japanese encephalitis virus, hepatitis C virus)	Dengue virus: Central and South America, sub-Saharan Africa, India, Southeast Asia, Pacific West Nile virus: North America, Europe, Russia, sub-Saharan Africa, Australia, New Zealand, Pacific Tick-borne encephalitis virus: Central Europe, Southeastern Europe, Baltic countries, southern Scandinavia, Russia, China, Korean peninsula Japanese encephalitis virus: East and Southeast Asia Hepatitis C virus: worldwide
Human immunodeficiency virus	Worldwide
Human T-cell lymphotropic virus	Japan, sub-Saharan Africa, Middle East, Caribbean, Central and South America
Picornaviruses (Coxsackie-, entero-, echoviruses, poliomyelitis virus, hepatitis A virus)	Coxsackie-, entero- and echoviruses, hepatitis A virus: worldwide Poliomyelitis virus: Africa, Middle East
Hepadnaviruses (hepatitis B virus)	Worldwide
Bacteria and spirochaetales	
Mycobacteria	Worldwide
Borrelia burgdorferi	Europe, North America, parts of Asia
Treponema pallidum	Worldwide
Staphylococcus, *Streptococcus*	Worldwide
Listeria	Worldwide (non-pasteurised milk products)
Mycoplasma	Worldwide
Chlamydophila spp.	Worldwide
Parasites	
Schistosoma spp.	*Schistosoma mansoni*: Central and South America, sub-Saharan Africa *Schistosoma haematobium*: sub-Saharan Africa *Schistosoma japonicum*: Southeast Asia
Taenia solium (larval stage: cysticercus cellulosae)	Central and South America, sub-Saharan Africa, South and Southeast Asia
Echinococcus granulosus *Gnathostoma spinigerum* *Toxocara spp.*	Middle East, South America, New Zealand Southeast Asia Worldwide

(continued)

Table 6.5 (continued)

Pathogen	Endemic region
Fungi	
Moulds, in particular *Aspergillus spp.*	Worldwide
Yeasts	Worldwide
Blastomyces dermatitidis	North America
Coccidioides immitis	United States (southwest), Mexico, Central and South America

Adapted from Trebst et al. [187]

6.2.2.2 Varicella Zoster Virus

Reactivation of varicella zoster virus (VZV) normally involves a single or more dermatomes and can be accompanied or followed by myelitis (Fig. 6.4). Myelitis can also occur during primary infection. Diagnosis is supported by PCR and antibody analysis in the CSF. Therapy is the same as for HSV myelitis.

6.2.2.3 Cytomegalovirus

Cytomegalovirus (CMV) infection/reactivation is particularly observed in immunocompromised individuals. CMV can cause a lumbosacral polyradiculomyelitis and also an LETM [167]. CSF examination reveals a mild to moderate pleocytosis and mild disruption of the blood–brain barrier. Diagnosis is assured by positive PCR amplification of CMV-DNA in the CSF. CMV infection/reactivation can also be monitored by analysis of pp65 antigen levels in peripheral blood samples, particularly in bone marrow transplant recipients [65, 178]. Therapy involves ganciclovir and foscarnet. Prognosis is poor.

6.2.2.4 Epstein–Barr Virus

Epstein–Barr virus (EBV) is the causative agent of mononucleosis and therefore mostly found in children and young adults. Initial infection can be followed after weeks with signs of a polyradiculomyelopathy. This is most often a postinfectious immune-mediated syndrome, and patients respond well to steroid therapy, which is often given in combination with aciclovir.

6.2.2.5 Human Herpes Virus

Very rarely, human herpes virus (HHV)-6 and HHV-7 may be the causative agent of myelitis, in particular, as a complication after bone marrow transplantation [4, 195].

6.2.3 Flaviviruses

Flaviviruses are transmitted by arthropods (ticks, mosquitoes) and have either no (dengue viruses) or well-defined mammalian (tick-borne encephalitis viruses, Japanese encephalitis virus) and/or avian (West Nile virus) hosts. They are subsumed under the term arboviruses, i.e. arthropod-borne viruses. They cause either

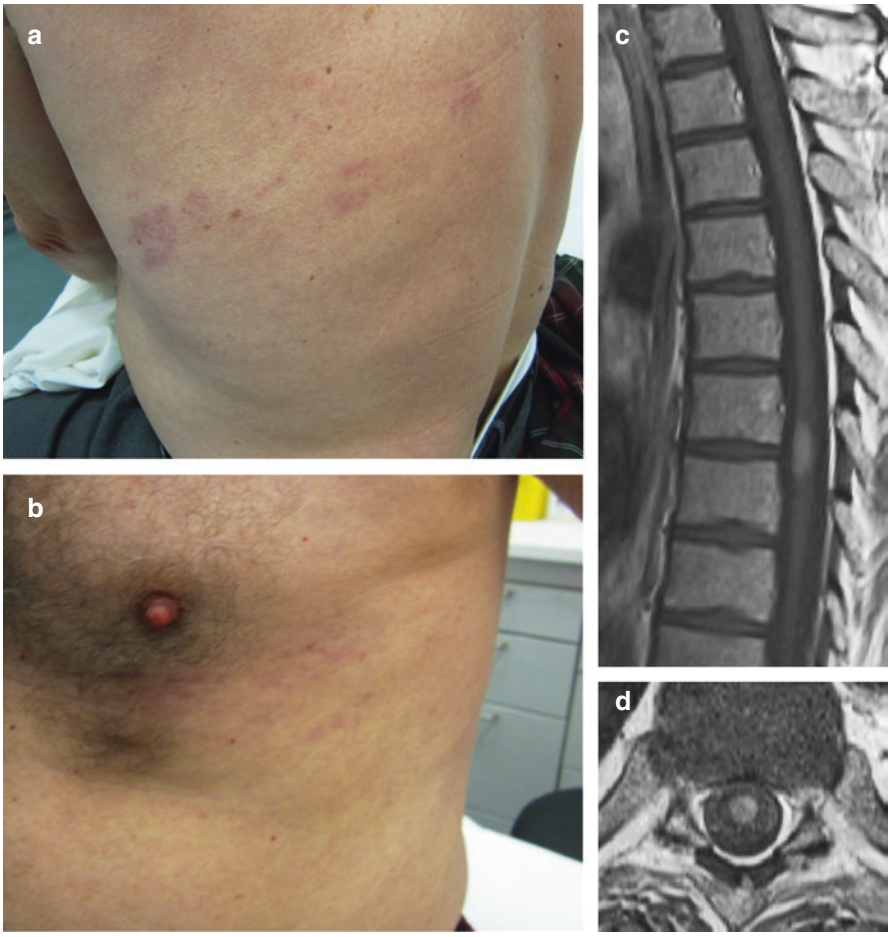

Fig. 6.4 VZV myelitis. (**a**, **b**) Herpes zoster skin lesion in a 70-year-old man presenting with paraparesis, urinary incontinence and sensory level Th7. T1-weighted (**c**) sagittal and (**d**) axial images of the thoracic spinal cord showing a well-demarked focal intramedullary lesion with gadolinium enhancement (Images courtesy of Prof. Erich Schmutzhard, Neurology, and Prof. Elke Gizewski, Neuroradiology, Innsbruck Medical University)

meningitis, encephalitis with special predilection for basal ganglia, or myelitis in which case they clearly show a predilection of the grey matter, i.e. of the anterior horns, causing a syndrome similar to poliomyelitis [75, 148].

6.2.3.1 Dengue Viruses

Dengue fever is a common arboviral infection in tropical and subtropical areas. Manifestations are increasingly recognised, but the exact incidence is still unknown [99, 193].

Dengue viruses are transmitted to humans by the bites of infective female *Aedes* mosquitoes (*A. aegypti*, *A. albopictus*, *A. scutellaris*, *A. polynesiensis*) with distinct

peculiarities in ecology, behaviour and geographical distribution [49]. Infected humans are the primary reservoir, thus serving as the principal source of the virus for uninfected mosquitoes. However, although uncommon, vertical transmission from mother to foetus, transfusion-related transmission, transplantation-related transmission and needle stick-related transmission have been reported.

The clinical manifestations of dengue fever ranges from an asymptomatic state to severe dengue and dengue haemorrhagic shock syndrome, caused by inflammation, capillary leakage and multiorgan impairment. Encephalitis and meningitis are the most frequent CNS manifestations [77]; rarely dengue viruses may cause myelitis, mainly poliomyelitis [5].

Dengue virus-related myelitis presents in MRI as diffuse signal intensity alterations in the spinal cord. Since – as other flaviviridae – dengue viruses mainly affect the grey matter of the spinal cord, particularly anterior horn cells, the acute clinical presentation is flaccid para- or tetraparesis, eventually evolving into spastic para- or tetraparesis [44]. In these cases, myelitis is probably caused by direct viral invasion, as indicated by intrathecal synthesis of dengue IgG antibodies [122, 144]. Diagnosis is confirmed by detection of the virus, viral nucleic acid, antigen or antibodies in the CSF. The level of suspicion is increased by the presence of other laboratory abnormalities as thrombocytopenia, progressive leucopenia and clinical signs of capillary leakage syndrome.

Dengue viral infections of the CNS are managed symptomatically; careful monitoring and maintenance of fluid and electrolyte balance is essential, aggressive management of fever may contribute to success as a neuroprotective measure. Non-steroidal anti-inflammatory agents should not be prescribed since they may aggravate the bleeding diathesis [69].

6.2.3.2 Tick-Borne Encephalitis Viruses

Up to 30,000 cases of tick-borne encephalitis (TBE) are estimated to occur annually in the European and Asian northern hemisphere [79], thus rendering TBE to the most important and most frequent zoonotic arboviral infection in this region [3]. In nature, TBE virus (TBEV) cycles between infected ticks and small mammals, mainly rodents. Transstadial and transovarial transmission of the virus occur. Beside tick bites, alimentary routes of TBEV transmission – by consuming raw milk or milk products, mainly of goats – are seen.

There are three viral subtypes, the Central European TBEV, the Eastern European subtype and the Siberian/Eastern subtype, the latter two are usually transmitted by *Ixodes persulcatus*, whereas *Ixodes ricinus* is the major vector of the Central European TBEV subtype. After the infective tick bite, the virus multiplies at the site of inoculation; dendritic cells of the skin transmit the virus to local lymph nodes from where infected lymphocytes initiate the systemic spread of the infection. Infection of the CNS can occur everywhere, however, most frequently and most intensely involving brainstem, cerebellum, basal ganglia, thalami and spinal cord, where mainly anterior horn cells are infected [18]. Typically, the disease runs a biphasic course; the majority of TBEV infections, however, remain asymptomatic. After an incubation period of 2–28 days, the first stage, i.e. viraemic phase, presents

with fever, muscle pains and fatigue. After an afebrile period of several days, the second phase starts mainly with meningitis, encephalitis (in older patients) and in up to 5–15 % with myelitis, most frequently presenting as poliomyelitis with flaccid paresis of the upper limbs [157].

No specific antiviral therapy exists; supportive measurements are most important to assure initial survival in patients with brainstem and encephalomyelitic involvement. CSF and MRI show unspecific changes; the diagnosis is confirmed by specific intrathecal antibody production [177]. Case fatality rate in tick-borne encephalitis depends on the initial clinical presentation being worst in the encephalitic and myelitic form. In Central European TBE, fatality rates are low (<2 %) [92], whereas in Siberian and far Eastern subtypes, fatality rates of >10 % have been reported.

In addition, long-term sequelae after TBE have been reported in 40–50 % in Western [92] and >60 % of patients in far Eastern and Siberian subtypes of disease [92, 177], and only 20 % of patients with TBE myelitis fully recover [91]. Active vaccination is recommended for TBEV-exposed persons in endemic regions.

6.2.3.3 West Nile Virus

West Nile virus (WNV) has first been described in Eastern Africa (West Nile province in Uganda) from where it has spread throughout the Eastern sub-Saharan African countries, towards Middle East countries, Balkan and, since around 15 years, towards the United States and Canada [68, 133, 164, 165]. Within the past 5 years, South European countries, in particular, Greece and Italy, and most recently even Central European Countries (e.g. Hungary, Italy, Austria) have reported autochthonous cases; [33]. The specific peculiarity of WNV infection is the transmission by mosquitoes, thus rendering WNV to the single most important mosquito-borne disease in temperate climates, e.g. the United States and Central Europe. The course of disease is very similar to TBE; however, in elderly and older subjects, a severe course of WNV neuroinvasive disease, i.e. encephalitis and myelitis, is seen more frequently. As in TBE, the myelitic course of WNV infection is predominated by affection of the anterior horn cells, thereby causing the clinical entity of a poliomyelitis type of disease [107, 113]. The presence of an intrathecal specific antibody production confirms the diagnosis of WNV neuroinvasive disease [45]. Management is supportive and includes all intensive care measures, when necessary [142]. In contrast to TBE, there is no protective vaccine available yet.

6.2.3.4 Japanese Encephalitis

Japanese encephalitis (JE) occurs in Asian countries ranging from Southeast China towards the Southeast and South Asian countries, including Nepal, India and small pouches in Pakistan. JE virus is transmitted by anopheles mosquitoes; the course is biphasic and frequently leads to encephalitis and also myelitis, where – similar to the other above-mentioned arboviral infections – the anterior horn cells are predominantly affected, thus causing a poliomyelitic course of disease. If the CNS is affected in JE, which occurs in <10 % of cases, the course of disease is much more

severe than in TBE or even in WNV encephalitis/myelitis. Case fatality rates of >30 % have been reported [179]. Diagnostic and supportive management strategies are similar to other viral encephalitis and myelitis [90]. A highly efficacious active vaccine exists; travellers to endemic areas, mainly during rainy season, when the mosquito activity is highest, are advised to get this protective vaccination, in particular, if they plan to stay for more than 4 weeks in this endemic area.

6.2.4 Retroviruses

6.2.4.1 Human Immunodeficiency Virus

The human immunodeficiency virus (HIV) is a ubiquitously occurring retrovirus accounting for a total of about 37 million infected individuals worldwide (http://www.who.int/gho/hiv/en/ of October 10th, 2016). Already during early infection, HIV can find its way into the CNS and cause an acute transverse myelitis. This is often categorised as an immune-mediated phenomenon and shows a good response to high-dose steroids and the start of antiretroviral therapy [70]. During further course of the disease, more chronic changes in the CNS are observed, particularly as encephalopathies but also as myelopathies. These are often characterised as slowly progressing gait disturbances and have to be distinguished from HIV- or antiretroviral therapy-associated neuropathies. Spinal MRI not always shows abnormalities, sometime only subtle changes of a beginning spinal atrophy or diffuse hyperintensities in the FLAIR and T2-weighted images with longitudinal extent and often restriction to the lateral and posterior thoracic cord [32] (Fig. 6.5). Diagnostic work-up should include exclusion of other infectious causes. Besides antiretroviral therapy regimes, no specific therapy applies for HIV myelopathy.

6.2.4.2 Human T-Cell Lymphotropic Virus Type 1

Human T-cell lymphotropic virus type 1 (HTLV-1) is endemic in Japan, sub-Saharan Africa, the Middle East, the Caribbean and Central and South America. Rarely sporadic cases are also observed in Europe and North America. HTLV-1 can cause a chronic meningomyelopathy. Diagnosis is based on MRI findings showing T2 longitudinal hyperintensities in the posterior and lateral columns of the cervical and thoracic cord as well as cord atrophy [101] and on CSF findings with mild pleocytosis, mild blood–brain barrier disruption and detection of HTLV-1 intrathecal antibody production. Treatment can only be symptomatic as a specific antiretroviral treatment does not exist.

6.2.5 Other Viruses

6.2.5.1 Poliomyelitis Viruses and Enteroviruses

Poliomyelitis viruses – being the aim of a global eradication campaign initiated in the early 1990s by the WHO – and a wide range of enteroviruses are small RNA viruses which are transmitted via the feco-oral route. It is mainly the fecal contamination of the environment [17] and the water supplies which constitute the major

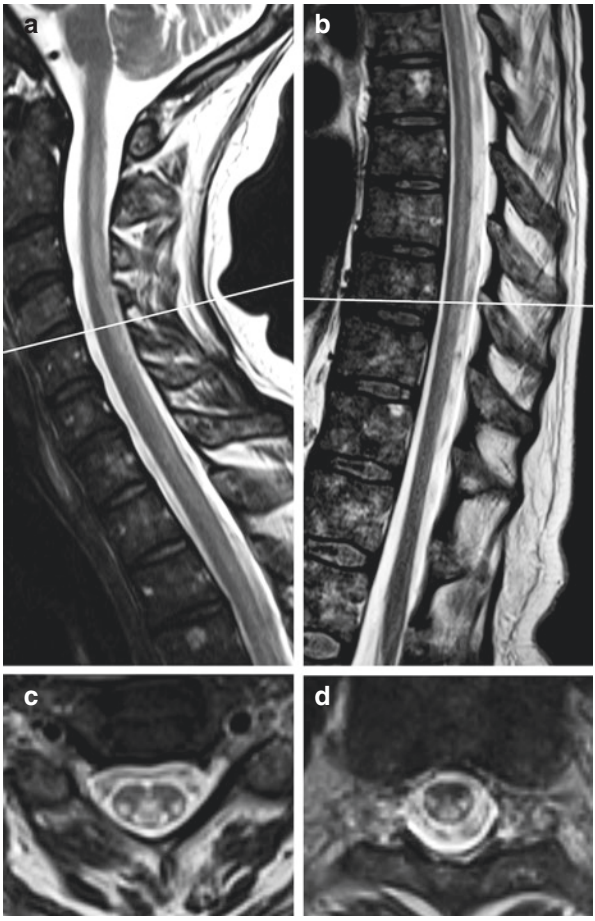

Fig. 6.5 HIV myelopathy. T2-weighted (**a**) cervical and (**b**) thoracic spinal MRI of a 43-year-old woman with a known HIV infection and a progressive paraparesis and gait ataxia are shown. (**c**, **d**) Note the longitudinal hyperintensities along the complete spinal cord with a restriction to the lateral and posterior cord. Lines indicate the sectional plane position of the axial images. Gadolinium enhancement was not found (images not shown) (Images courtesy of Dr. Peter Raab, Neuroradiology, Hannover Medical School)

transmission pathways, rendering the envisaged global eradication of wild-type poliovirus so difficult and a major technical and political challenge [62, 124].

Poliomyelitis still exists in Afghanistan, Pakistan, parts of India, Nigeria, Somalia and parts of northern Kenya; most recently wild-type virus has been detected in Israel [93, 104] and a small epidemic has also been reported from war-stricken Syria. Three serotypes of wild-type polioviruses exist in nature, all of them similarly transmissible and potentially causing disease in man.

The course of disease in case of poliomyelitis virus infection may be rather diverse, ranging from unspecific flu-like signs and symptoms being associated with

gastrointestinal discomfort – in the majority of cases – to most severe courses with encephalitis and poliomyelitis, i.e. anterior horn cell myelitis. Such patients develop acute flaccid mono-, para- or tetraparesis, frequently associated with painful radiculitis. In the initial phase, the flaccid paresis may be associated with loss of deep tendon reflexes, leading to rapid atrophy of muscles, being associated with joint contractures, shortening of tendons and inability to normal development of the limbs. In areas where the disease has been almost eradicated, newly developing epidemics might affect not only children but also younger adults.

In an Australian cohort, out of more than 1300 isolates from patients suffering from acute poliomyelitis, 53 % were confirmed as Sabin vaccine like poliomyelitis virus, 41 % were non-polio enteroviruses and 6 % other enteroviruses. This finding indicates that outside the known geographical foci in Afghanistan, Pakistan, Nigeria, Somalia and Kenya, the occurrence of poliomyelitis is very rarely due to a wild-type poliovirus (serotypes 1, 2, 3) but mostly due to Sabin vaccine like poliovirus or non-polio enterovirus (mainly enterovirus 68,69,70). In rare cases, also Coxsackie viruses and other enteroviruses may cause a poliomyelitis-type disease [117]. Enteroviruses 69, 70 and 71 caused epidemics of viral haemorrhagic conjunctivitis; in such an epidemiologic and clinical setting, polio-like signs can be usually attributed to these enteroviruses [33, 116, 134, 135].

Poliomyelitis due to wild-type polioviruses can easily be prevented by vaccines, both oral and parenteral (Sabin and Salk vaccines, respectively). Rarely, the oral polio vaccine (Sabin) may cause a wild-type polio-like disease in immunocompromised patients (e.g. pregnant women) if these patients get infected via the feco-oral route or contact (feco-oral contact) with newly vaccinated children. However, this oral polio vaccine strategy has contributed and still contributes to a very high level of herd immunity; therefore, it is still widely used in the global polio eradication campaign.

6.2.5.2 Rabies Virus

Rabies is a fatal infectious disease of the nervous system, mainly transmitted to humans and animals through bites of rabid animals, in particular dogs, foxes and bats. In up to 20 %, rabies runs an atypical paralytic form, difficult to distinguish from Guillain–Barré syndrome (GBS) or myelitis. The diagnosis of this course of disease is particularly difficult when the history is concealed or not remembered anymore. The latter fact can easily be understood since the incubation period of rabies may be months or even years. Imaging of rabies myelitis has been shown to involve mainly the grey matter of the spinal cord, very similar to poliomyelitis. The white matter is relatively spared [51, 191]. Nevertheless, a clear-cut neuroimaging clue does not exist; therefore, the appropriate history and a high level of suspicion are necessary to timely diagnose the flaccid (=silent) form of rabies. This is of utmost importance since rabid humans are equally infective as are rabid animals. The prognosis of any type of rabies is bleak, i.e. invariably fatal.

6.2.5.3 Mumps, Measles, Rubella and Influenza Viruses

All these viral diseases have been shown to cause in rare cases involvement of the spinal cord by direct viral invasion [171]. However, more frequently postinfectious/parainfectious diseases are seen [7, 23, 36]. The diagnosis is made easily if the

clinical entity of the respective viral disease (mumps, measles, etc.) is clearly associated with the myelitic signs and symptoms and within the epidemiologic setting of a measles, mumps [8] or influenza outbreak [199].

6.2.5.4 Hepatitis Viruses

Single cases of myelitis have been reported in or after infection with hepatitis A, B and C virus [170]. Detection of viral DNA or RNA in the CSF [80, 176] or of a specific intrathecal antibody production [56, 97] is diagnostic.

6.2.6 Neuroborreliosis

Borrelia burgdorferi is the causative agent of neuroborreliosis or Lyme disease. It is transmitted by the *Ixodes* tick species and endemic in the northern hemisphere (Europe, North America) and Asia. Early infection usually shows dermatological changes at the site of the tick bite with an erythema chronicum migrans. In the next stage (stage II), mainly cranial nerve palsies (typically N. VII) and painful meningoradiculitis (Bannwarth's syndrome) are observed. Transverse myelitis can be a rare manifestation in this stage (Fig. 6.6). It represents less than 5 % of all cases of neuroborreliosis in larger series [72, 131]. A more chronic and progressive myelopathy in late neuroborrelioses has also been described [31]. Neuroborreliosis has no specific MRI abnormalities, with multiple sclerosis being a common differential diagnosis. Diagnosis is based on CSF analysis showing a mild to moderate pleocytosis, often with mixed cytology, and high amounts of plasma cells and elevated levels of CXCL13 in the CSF [127, 151, 168]. Calculation of specific intrathecal antibody synthesis against *Borrelia burgdorferi* using ELISA screening tests and Western Blot validation is pertinent for the diagnosis of neuroborreliosis. Serum/blood testing alone is not sufficient. A missing pleocytosis but signs of intrathecal antibody synthesis should be interpreted with caution and are most often evidence for a history of infection. Therapy of choice is IV ceftriaxone for at least 14–21 days, in stage II oral doxycycline (100 mg twice daily) for 14 days can also be chosen [50]. With adequate antibiotic therapy, there is often a full recovery of myelitis.

6.2.7 Neurosyphilis

Clinical picture and manifestation of an infection of the CNS with *Treponema pallidum* are manifold. The most frequently reported clinical manifestation in a Dutch survey was tabes dorsalis [41]. Individuals with tabes dorsalis show sensory gait ataxia and lancing pains. MRI reveals cord atrophy and often hyperintensities in the dorsal roots and posterior columns of the lower thoracic cord [136]. Diagnosis is based on serological and CSF findings demonstrating an intrathecal antibody production. Particularly, the diagnosis is certain with a positive CSF VDRL testing [74]. If the VDRL is negative, a positive FTA-ABS associated with raised CSF cell count, protein or IgG index is a useful method of identifying neurosyphilis [181]. Therapy is long-term and high-dose IV penicillin.

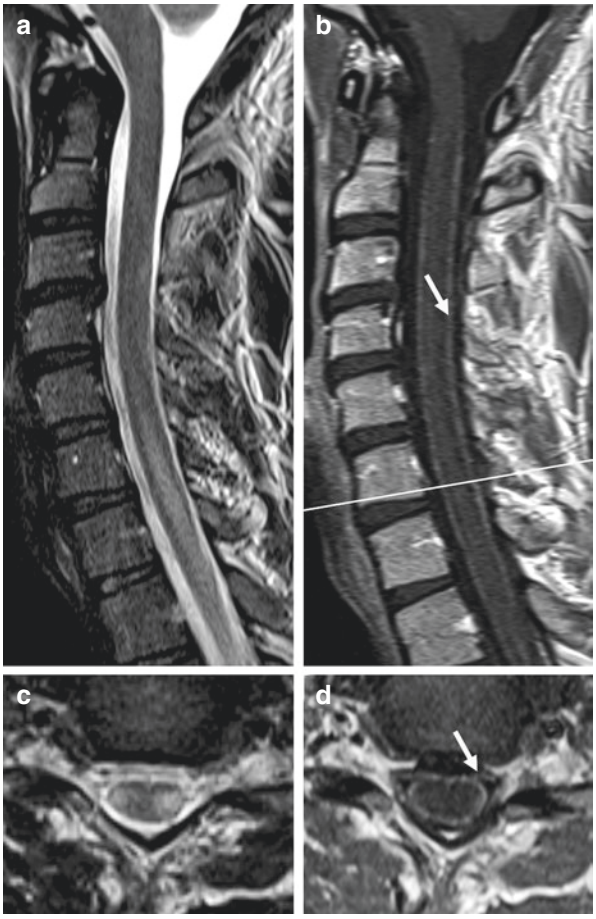

Fig. 6.6 Neuroborreliosis. This 37-year-old man had a yearlong history of a progressive gait disturbance when presenting for diagnostic work-up. The spinal MRI disclosed a multisegmental myelitis and meningoradiculitis with gadolinium enhancement of the meninges and anterior and posterior horn roots (*arrows*). (**a**, **c**) T2w-TSE images, (**b**, **d**) T1w-SE images with gadolinium. CSF revealed a pleocytosis and signs of an intrathecal antibody synthesis against *Borrelia burgdorferi*. After 3 weeks of IV ceftriaxone, the patient made a full clinical and radiological recovery (Images courtesy of Dr. Peter Raab, Neuroradiology, Hannover Medical School)

6.2.8 Bacterial Infections of the Spinal Cord

6.2.8.1 Mycobacteria

Infection with *Mycobacterium tuberculosis* is second only to HIV/AIDS as the greatest killer worldwide due to a single infectious agent. In 2014, 9.6 million people fell ill with tuberculosis, and 1.5 million died from it. Over 95 % of the deaths occurred in low- and middle-income countries, but tuberculosis has increasingly been diagnosed also in the developed countries and is becoming a

major disease burden (http://www.who.int/gho/tb/en/ of October 10th, 2016). Infection of the CNS with *Mycobacterium tuberculosis* or *Mycobacterium avium* is most commonly meningitis, but intramedullary or intradural extramedullary tuberculomas have been observed [185]. CSF examination typically reveals mild to moderate pleocytosis and severe disruption of the blood–brain barrier. Specific pathogen diagnostics are possible with culture and PCR amplification techniques. Treatment has to be long term starting with a quadruple tuberculostatic therapy (for up to 6 months) and then continuing with a triple therapy for a total of up to 2 years. A rarely described and poorly understood clinical entity is the mycobacterial myelopathy, most likely direct intramedullary infection playing the major part of pathogenicity. Steroid therapy has been shown to be not more effective than long duration of mycobacterial chemotherapy, most likely being necessary for a minimum of 2 years [53].

6.2.8.2 Mycoplasma, Chlamydophila and Bartonella

Mycoplasma pneumoniae and *Chlamydophila spp.* (e.g. *Chlamydophila pneumoniae*, *Chlamydophila psittaci*) may cause parainfectious myelopathies. In rare cases, direct invasion of the endothelial cells of arteries and arterioles serving the spinal cord has been described [66, 200]. Only few cases of myelitis presenting as Brown-Sequard syndrome have been described after cat scratch disease due to *Bartonella henselae* [25]. Long-term antibiotic therapy with doxycycline, macrolide antibiotics or gyrase inhibitors is needed; however, the evidence on efficacy, duration of therapy and long-term sequelae is scarce [188].

6.2.8.3 Brucella

Infection by one of the four main subtypes of *Brucella spp.* causes the zoonotic brucellosis. *Brucella melitensis*, *Brucella abortus Bang* and *Brucella suis* (in recent years also *Brucella ovis*) cause a systemic infectious disease; the bacteria are transmitted to humans from infected animals, e.g. goats, sheep, pigs, cows or camels. High-risk areas include mainly the Middle East/Mediterranean region but also Central and South America and sub-Saharan Africa. Infection occurs usually by consumption of unpasteurised milk or milk products, but also veterinarians, butchers, hunters or laboratory workers are at risk. After a prolonged generalised disease with anorexia, headache, myalgia and intermittent undulating fever, organ malfunction and involvement of the CNS may occur [37]. One of the most frequent and most serious complications of *Brucella spp.* infection is spondylitis which may occur in up to 50 % of cases with systemic infection [95]. Lesions may affect all levels of the vertebral spine, most commonly however, the lumbar spine at the level L4–L5 [61]. Adjacent granuloma and abscess formation causes epidural space-occupying lesions and compression of the spinal cord and nerve roots. Granuloma may also develop within the spinal cord. The diagnosis is based upon clinical history, history of exposure and a long-standing preceding generalised disease, local pains and focal neurological findings. Diagnosis is supported by serology, blood culture and culture from biopsies. Isolation of bacteria from tissue and blood is successful in up to 70 % of cases. Beside neurosurgical decompression, treatment

of neurobrucellosis comprises of an antimicrobial chemotherapeutic combination of rifampicin and doxycyclin, minimum 6 weeks. To avoid common relapses, intramuscular streptomycin has been recommended to be added in myelitis, spondylitis or endocarditis [106]. Seroconversion, negative blood cultures and improvement in neuroimaging and of clinical signs and symptoms indicate resolution of the disease, supporting the decision to stop the combination antimicrobial chemotherapy.

6.2.8.4 *Listeria Monocytogenes*, Staphylococci and Streptococci

Listeria monocytogenes, staphylococci and streptococci have been described to cause – in rare cases – intramedullary infection, including abscess formation. The direct visualisation of the pathogenic agent by computed tomography-guided biopsy allows the diagnosis, including microbiological work-up of the material, and appropriate therapy [26, 128].

6.2.9 Schistosomiasis

Parasitic or fungal causes of myelitis are rare but should be considered when myelitis occurs in habitants or travellers in endemic regions [161]. *Schistosoma* are endemic in Central and South America (*Schistosoma mansoni*) and sub-Saharan Africa (*Schistosoma mansoni* and *Schistosoma haematobium*). Myelopathy of the lumbosacral region is the most common neurological complication of *Schistosoma mansoni* and *Schistosoma haematobium* infection [54]. MRI shows longitudinal extensive myelitis and cord swelling and heterogeneous contrast enhancement [55] (Fig. 6.7). Specific diagnosis can be based on serological testing, evidence of *Schistosoma* infection and identification of parasite antigens in blood or CSF [64]. Therapy consists of praziquantel and steroids. Complete or partial recovery is observed in most of the patients. Early diagnosis and prompt treatment are essential [150].

6.2.10 Eosinophilic Radiculomyelitis Caused by Nematode Larvae Migrantes

Third-stage larvae of *Gnathostoma spinigerum* (Southeast Asia), *Angiostrongylus cantonensis* (Southeast Asia), *Angiostrongylus costaricensis* (Central America), *Toxocara canis* (worldwide) and *Baylisascaris procyonis* (North America) have the capacity to cause the clinical entity of a larva migrans syndrome [115, 159]. Potentially, the larvae invade the subarachnoid space, radices and myelon [52, 83, 96, 152, 158]. The disease is characterised by usually acute, rarely subacute, onset of radicular or intramedullary signs and symptoms [78]. Human infection by the nematode larva of *Gnathostoma spinigerum* results from eating raw fish, snails, shrimps, frogs or insufficiently cooked chicken or duck meat contaminated with larvae of this parasite [148, 158]. Dogs, cats and pigs are the definitive hosts. After ingestion, the highly motile larvae migrate through all deep and subcutaneous

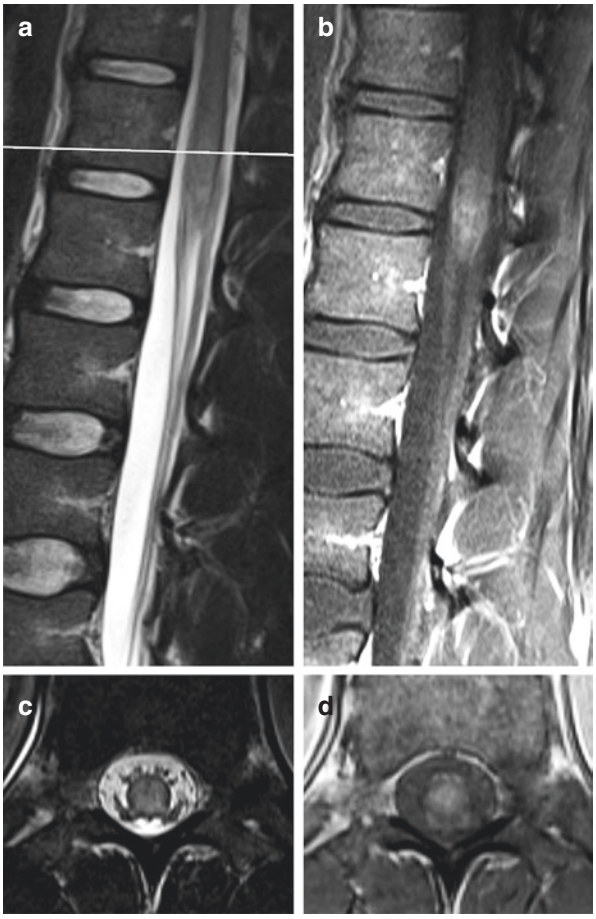

Fig. 6.7 Schistosomiasis. A 24-year-old male Brazilian student was visiting Germany when developing a conus/cauda syndrome. The spinal MRI shows a longitudinal myelitis with predominant involvement of the conus medullaris with patchy gadolinium enhancement. Diagnosis of schistosomiasis was based on positive *Schistosomiasis mansoni* antibody testing. A full recovery was achieved by treatment with praziquantel. (**a**, **c**) T2w-TSE images, (**c**, **d**) T1w-SE images with gadolinium (Images courtesy of Dr. Peter Raab, Neuroradiology, Hannover Medical School)

tissues with specific neurotropism. Whereas *Gnathostoma spinigerum* frequently causes long haemorrhagic tracts from nerve roots to the myelon and even brainstem, all the other larvae migrantes only rarely invade the brainstem or myelon [108, 189]. If they do, the onset and course of disease is less fulminant, frequently also accentuated by granuloma formation [132]. This might create difficulties in differentiating such a granuloma from a tumour, tuberculoma, etc. Typically, eosinophilia is found to be more pronounced in gnathostomiasis but may also be present in the other nematode larval meningitis or myelitis manifestations [94]. Albendazole may be used to kill these larvae migrantes; however, concomitant steroid therapy might be necessary to alleviate toxic or allergic reactions with clinical deterioration.

6.2.11 Neurocysticercosis

Involvement of the spinal cord by the larvae of *Taenia solium* (pig tapeworm) is very rare, even in endemic areas, such as Latin America, sub-Saharan Africa or South and Southeast Asia. If humans ingest *Taenia* eggs (due to fecal contamination of food, water or autoinfection in case of intestinal taeniasis), they become intermediate hosts, thus being prone to develop the clinical entity of cysticercosis. In tropical areas, up to 50,000 deaths are attributed to neurocysticercosis, mainly due to intracranial cyst formation, leading to severe encephalitic brain oedema, space-occupying lesions and epilepsy, even intractable status epilepticus [47]. In less than 0.2 % of infections, the spinal canal or the spinal cord is involved; usually the space-occupying effect of the cysticercal cysts is responsible for spinal neurocysticercosis. Spinal neurocysticercosis may be associated with cauda equina or Brown-Sequard syndrome, and CSF findings might be similar as in eosinophilic meningitis [183]; however, in pure cyst formation, eosinophilia may also be absent. The diagnosis is confirmed by neuroimaging and serology, which should include ELISA for cysticercus cellulosae antigen thereby confirming an active neurocysticercosis [59]. Anthelmintic therapy is – at least in cerebral neurocysticercosis – a combination therapy with praziquantel and albendazole. Concomitant dexamethasone administration should begin prior to the anthelmintic therapy and should be prolonged for up to a week beyond the termination of anthelmintic drugs. In specified cases, neurosurgical intervention might be necessary.

6.2.12 Fungal Myelopathies

Involvement of the spinal cord with fungal pathogens is exceedingly rare [100]. Both compressive myelopathy due to vertebral osteomyelitis and granulomatous meningitis and spinal cord infarction due to meningovascular infiltration [139] have been described in patients with *Blastomyces*, *Histoplasma*, *Coccidioides immitis*, *Aspergillus spp*., *Candida spp*. and *Cryptococcus spp*. infection [21, 28, 43, 67, 87, 118, 137, 145, 153]. Direct visualisation of the pathogenic agent is essential to allow for the best possible specific antimycotic chemotherapy [73, 160]. No evidence is available as to dosage and duration of antimycotic chemotherapy. Recently, in the United States, direct inoculation of an otherwise non-pathogenic fungus into the subarachnoid space by contaminated steroid injections has caused an epidemic of *Exserohilum rostratum* CNS infections [27, 29].

6.2.13 Diagnostic Work-Up

The diagnostic work-up of pathogen-caused myelitis is following the same routines as for immune-mediated myelitis. Besides early gadolinium-enhanced MRI of the spinal cord to rule out a compressive aetiology, the analysis of the CSF is the cornerstone of the diagnostic work-up. A pathogen-driven myelitis should be suspected

in cell counts >50 cells/μL. Pleocytosis and a disruption of the blood–brain barrier are often observed. PCR amplification of viral DNA or RNA allows specific identification of the causative agent [173]. The additional analysis of the humoral response and the calculation of an antigen-specific antibody index as sign for a specific intrathecal immunoglobulin production are helpful, particularly in PCR-negative settings. Bacterial pathogens are mostly identified by culture of the CSF or when bacteraemia is present in blood cultures. In addition, PCR amplification is helpful in identifying infections with mycobacteria. Analysis of the humoral response and calculation of an antigen-specific antibody index are essential for the diagnosis of neuroborreliosis and neurosyphilis (see above).

6.2.14 Therapeutic Strategies

Therapeutic strategies are first of all anti-infective. Depending on the identified pathogens, antiviral, antibiotic, antiparasitic or antifungal treatment regimens have to be chosen (details listed above). Concomitant steroids can be given in most of the pathogen-caused myelitis cases [119].

Conclusions

Myelitis can be caused by infections, autoimmunity and other immune-mediated mechanisms including para-/postinfectious and paraneoplastic aetiologies. Differential diagnosis is guided by clinical history, neurological examination, CSF analysis and spinal MRI. Due to advances in imaging and laboratory techniques, particularly identification of new autoantibodies and methods for humoral and nucleic acid detection of pathogens, these diseases are increasingly diagnosed in clinical practice. Infectious and autoimmune myelitis are associated with significant morbidity and mortality and often account for severe neurological deficits and long-term sequelae; therefore, early and specialised multidisciplinary care are recommended.

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Spinal Cord Compression

7

Peter Prang

Abstract

Spinal cord compression (SCC) occurs when degenerative spine disease, metastatic or primary spine tumors, hematoma, infectious lesions, or other etiologies pressurize the epi- or intradural space and therefore the spinal cord. The exact incidence and prevalence of SCC remain unknown. Neck or back pain is a common symptom of the clinical presentation. Radicular pain and symptoms of spinal cord dysfunction such as weakness, sensory disturbances, and bowel and bladder dysfunction typically follow. For diagnosis magnetic resonance imaging (MRI) is the method of choice. MRI visualizes the structures around the spinal column and the intrinsic aspects of the cord adjacent to the lesion. In certain conditions like neoplasms, computed tomography (CT) is necessary to assess osteolytic destruction, which may cause instability of the spine. The clinical diagnosis of acute SCC without delay is critical because patient outcome heavily depends on timely decompression strategies. Neurological function at the time of treatment is an important outcome predictor, and, if diagnosis is missed, patients may have further neurological deterioration. Treatment principles for patients with SCC should aim for improvement or preservation of neurological function keeping the patient's underlying disease burden in mind. In patients with neoplastic SCC, surgery and radiation therapy are common therapeutic options. Systemic therapy may be beneficial in patients with chemosensitive malignant tumors. Evacuation of a hematoma by surgical decompression remains the treatment of choice in patients with a relevant neurological deficit. Antimicrobial therapy and surgical management are the treatment options of choice for empyema caused SCC.

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7.1 Cord Compression by Degenerative Spine Disease

Degenerative spine disease includes spondylotic myelopathy, compression of the cauda equina and disk herniation. This condition represents an almost universal sequel of aging, which remains often asymptomatic. However, spinal cord compression can promote severe neurological deficits.

7.1.1 Spondylotic Myelopathy and Compression of the Cauda Equina

Spondylosis starts with degenerative biochemical changes in the intervertebral disks leading to destabilization of the posterior joints. Reactive bone proliferation occurs resulting in the formation of osteophytes which in combination with hypertrophy and ossification of the posterior longitudinal ligamentum and ligamentum flavum may compress the nerve root canal or narrow the spinal canal. Compression of the spinal canal causes myelopathy of the cervical/thoracic spinal cord or cauda equina compression in the lumbar spine. Hypermobility of the degenerative altered facet joints may lead to spondylolisthesis and intermittent neural compression. In particular the spondylotic myelopathy of the cervical spinal cord represents a very common cause of spinal dysfunction in the elderly population [1]. In the North American region, the incidence and prevalence of spinal cord compression caused by degenerative cervical myelopathy are estimated at minimum 41 per year and 605 per 1 million, respectively [2].

In contrast, congenital spinal stenosis is based on a developmental narrowing of the spinal canal. The spinal canal is narrowed much more uniformly, whereas degenerative changes like osteophytic or soft tissue overgrowth are not common. Patients present similar symptoms like patients with degenerative spinal stenosis. However, the onset of clinical signs is earlier, typically between the fourth and sixth decade [3].

Patients with cervical spondylotic myelopathy complain of neck pain or stiffness, numb and/or clumsy hands, weakness, bilateral arm paresthesia, and gait impairment, which may be determined by a sensory impairment in particular a reduced position and vibration sense, lower extremity ataxia, or a spastic gait pattern. Furthermore, in the clinical examination, hyperreflexia, corticospinal tract signs, and also an increased muscle tone in the upper extremities may be found. But also weakness in the hand muscles with concomitant muscular atrophy can indicate a cervical myelopathy. In the clinical course, patients may develop autonomic symptoms including increased urinary urgency, voiding frequency, and incontinence [4].

Lower extremity or buttock pain often in combination with back pain also known as neurogenic intermittent claudication is typical for a cauda equina compression due to spondylotic narrowing of the lumbal spinal canal. Patients sit down or bend forward because these movements widen the spinal canal, reduce pressure to neural structures, and as a consequence relieve symptoms. In more severe cases, the maximum walking distance is reduced, and patients develop a permanent sensory impairment and a progressive lower motoneuron-type paraparesis with bladder and bowel dysfunction.

Besides disk degeneration altered facet joints, hypertrophy of the ligamentum flavum, the posterior longitudinal ligamentum, and osteophytes contribute to a degeneratively narrowed spinal canal. Degenerative spondylolisthesis, which may also cause narrowing of the spinal canal, can be visualized in sagittal T2-weighted images. Typically, MR images demonstrate a cervical spinal canal characterized by multisegmental ventral and dorsal narrowing. Myelopathy is identified by a hyperintense signal change in the cord center (Fig. 7.1). Sagittal T2-weighted MR images also reveal a degenerative altered lumbar spinal canal resulting in cauda equina compression. Axial images show the width of the spinal canal. A relative stenosis is defined by a midsagittal diameter of the spinal canal <12 mm, whereas the diameter of an absolute stenosis is less than 10 mm [3].

The usual clinical course of spondylotic myelopathy is variable. Periods without clinical symptoms alternate with symptomatic periods, which complicate the

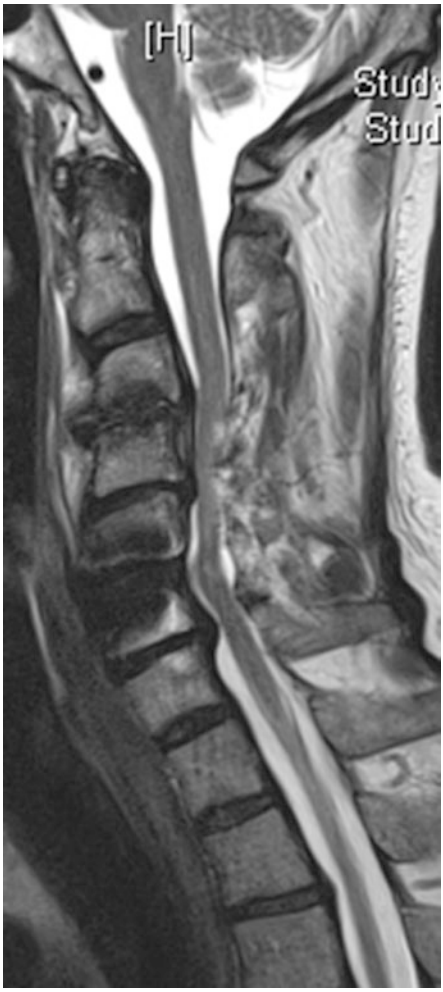

Fig. 7.1 Cervical spondylotic myelopathy: Sagittal T2-weighted MR image showing a multisegmental degenerative narrowing of the spinal canal at cervical level with depleted subarachnoid space and a hyperintense intramedullary signal reflecting myelopathy with maximum at level C4/C5 in a 50-year-old patient with tetraparesis C3 (AIS D)

treatment management. Conservative treatment options include physical therapy, analgesic drugs, and cervical orthoses. Nonoperative treatment strategies of cervical spondylotic myelopathy with regular reassessment represent the preferred option in cases with mild to moderate symptoms [5–7]. In contrast, results from a recent prospective multicenter cohort study suggest that the status of patients with cervical decompression may improve – even in patients with mild symptoms – in respect to function, participation, and quality-of-life at 1-year follow-up. In this study investigator-administered indices (mJOA scale and Nurick grade), which quantify the severity of functional and neurological impairment in patients with spondylotic myelopathy, and self-reported indices like the Neck Disability Index and Short Form-36 Version 2, were used for assessment [8]. In patients with progressive and moderate to severe neurological impairments, surgical decompression should be considered and can be performed anteriorly or posteriorly. The main goal is to remove compressing structures in order to provide sufficient space for the spinal cord. Furthermore stabilization of segments with increased mobility should be performed to prevent spine deformities. Discectomy and corporectomy and fusion are common techniques used in the anterior approach, while laminectomy with or without fusion is performed posteriorly [9].

In case of lumbar spinal stenosis, decompression by laminectomy is commonly performed [10] through removal of posterior spine structures like laminae, facets, ligaments, or osteophytes. After these procedures, an instability of the spine may develop over time requiring spinal fusion or implants. It has yet to be determined whether surgical or conservative treatment is superior in patients with lumbar spinal stenosis. Surgery-related complications have been reported in up to 24 % as opposed to a conservative regimen. Of course, noninvasive treatment programs including physical therapy, medication, exercise, manipulation, mobilization, acupuncture, and cognitive-behavioral therapy show little to no side effects [11].

7.1.2 Disk Herniation

Disk herniation in the thoracic spinal column represents a rare disease condition. The incidence of a symptomatic thoracic disk herniation is around one in 1,000,000 persons per year in the general population [12, 13]. In the midline of an intervertebral disk, the posterior longitudinal ligament strengthens the annulus fibrosus. As a consequence, a disk herniation usually occurs more laterally and rather compresses nerve roots. A medial disk herniation with consecutive cord compression causes a myelopathy or a compression of the cauda equina of the lower lumbar spinal cord [14].

The onset of clinical signs may be either acute within hours or slowly progressive over weeks or months. Typically patients suffer from neck or back pain followed by progressive numbness and weakness in the limbs. Bladder dysfunction may occur. In severe cases, painless urinary retention and overflow incontinence are common. In more incomplete conditions, an altered sensation of bladder filling, loss of urge to void, and voiding problems with associated residual urine in the bladder are early clinical signs. Furthermore, bowel and sexual dysfunction can be observed. Compression of the cauda equina by a lower lumbar disk herniation, prolapse, or

sequestration mostly occurs at the L4/L5 or L5/S1 vertebral level and presents with severe lower back pain, bilateral sciatica, and sensory and motor deficits according to the affected lumbosacral roots. In particular, saddle and genital sensory disturbance are typical signs of cauda equina syndrome. Bladder, bowel, and sexual dysfunctions are found in severe cases. Both clinical courses with a rapid onset without a previous history of back pain or gradually progressing symptoms with chronic back pain and sciatica have been described [15].

Disk herniation is a space-occupying process, which depletes the ventrodorsal subarachnoid space typically found in sagittal or axial T2-weighted MR images. An intramedullary hyperintense signal caused by edema of the spinal cord indicates the myelopathy [16].

In case of neurological impairment caused by compression of the spinal cord or cauda equina, surgical decompression is recommended [16, 17]. Discectomy in combination with a ventral fusion is typically performed in patients with fast progressing neurological deficits caused by a cervical disk herniation [14]. In cauda equina compression caused by disk herniation, a dorsal decompression is performed by hemilaminectomy or laminectomy including a discectomy [18, 19].

7.1.3 Adjacent Segment Disease (ASD)

Adjacent segment disease includes various complications of spinal fusion including listhesis, herniated nucleus pulposus, facet joint degeneration, or vertebral compression fracture with instability of the spine. In severe cases, these conditions can cause a compression of the spinal cord or cauda equina. Adjacent segment disease is caused by biomechanical stress leading to degenerative processes in adjacent segments post fusion. Increased motion at adjacent segments causing increased intradiscal pressure is one reason for ASD. ASD only occurs in a certain population of patients after spinal fusion. Various risk factors have been identified, which can be categorized in preexisting conditions and surgery-related variables. One of the most important risk factors is age at the time of fusion, because of the ongoing disk degeneration in combination with an impaired ability of the spine to adapt to biomechanical alterations caused by a spinal fusion [20]. Furthermore, preexisting degenerated disks or facet joints in adjacent segments or osteoporosis are known as predisposing conditions. Nonphysiological sagittal alignment after surgery introduces biomechanical stress and can be another cause for ASD. After anterior cervical fusion with a plate, the distance between the plate and adjacent segments may influence the amount of ossification and degenerative changes at adjacent segments [21]. The number of fused segments does not necessarily correlate with increased incidence in ASD. Also the fusion method has no clear impact on ASD incidence [22]. Alterations confirmed by Radiographic changes in plain x-ray or CT scans of adjacent segments are common but do not correlate with clinical symptoms. Clinical symptoms are sustained back pain followed by sensory deficits, bladder and/or bowel dysfunction. The combination of clinical and radiological findings defines the treatment strategy. Treatment options for ASD include extension of the number of fused vertebrae and/or decompression [23].

7.2 Cord Compression by Neoplastic Diseases

Tumors compressing the spinal cord are commonly divided into epidural neoplastic diseases (primary neoplasms and metastases), intradural extramedullary malignancies, and intramedullary tumors.

7.2.1 Epidural Tumors and Metastases

Primary spinal benign and malign neoplasms originate from osteocytes, osteoblasts, chondrocytes, fibroblasts, and hematopoietic cells of the vertebral body and surrounding structures. Primary spinal tumors are rare. Only 0.5 % of all spinal neoplastic diseases are primary tumors and mostly affect patients older than 40 years.

7.2.1.1 Hemangioma

One of the most common benign tumors of the vertebral column is the vertebral hemangioma. This extremely vascularized and slowly growing neoplasm is characterized by vascular tissue proliferation of endothelial origin [24]. This tumor is predominantly located in the vertebral bodies of the thoracic spine. In most cases, vertebral hemangiomas are asymptomatic and therefore diagnosed incidentally [25]. Rarely, they may cause back pain or neurological impairments caused by spinal root and/or cord compression by a bony expansion or compression fracture of the vertebral body [26]. CT scans are mandatory to evaluate the grade of osteolytic destruction, which may lead to instability of the affected spine. MRI typically shows a hyperintense signal change in T1- and T2-weighted sequences within the vertebral body. Depending on the severity of the clinical symptoms, a number of treatment modalities exist including radiotherapy, vertebroplasty, embolization, and surgical decompression with spinal fusion. In instances, where a hemangioma does not cause clinical symptoms and does not lead to spine instability, no special treatment is required. In case of open surgery, a preoperative angiography with embolization should be considered to avoid a significant perioperative bleeding due to high grade of vascularization.

7.2.1.2 Osteoblastoma, Osteochondroma, Chondrosarcoma, Osteosarcoma, and Ewing Sarcoma

A variety of less common tumors originating in the spine can expand in the epidural space and cause spinal cord compression. Unremitting neck or back pain followed by neurological deficits depending on the localization of the tumor like radiculopathy, myelopathy, or cauda equina syndrome are typical clinical signs. Patients with more aggressive tumors like osteosarcoma and Ewing sarcoma will develop neurological dysfunctions more frequently and earlier in the clinical course.

Osteoblastoma predominantly found in young men is in most cases a benign slowly growing neoplasm, which produces osteoid and is histologically characterized by a nidus comprising a vascularized bony matrix. The most common initial clinical sign is back pain. CT scan reveals multiple small calcifications in combination with a sclerotic rim. Bone destruction with matrix calcification and paravertebral expansion is typical for more aggressive types of osteoblastomas.

Osteochondroma is a benign neoplasm, predominantly of the cervical spine in male patients, defined as a cartilage-covered osseous excrescence of a parent bone. A marrow and cortical continuity to the parent bone is pathognomonic for osteochondromas revealed by thin-section CT [27]. MRI can visualize the hyaline cartilage cap. A thickness of more than 1.5 cm is suspicious for malignant transformation to a chrondrosarcoma. En-bloc-resection is considered the standard therapy for osteoblastoma and osteochondroma.

Chondrosarcoma is a common non-lymphoproliferative primary malignant neoplasm of the spine in adults and mainly found in the thoracic spine. Tumor cells produce a typical mineralized chondroid matrix forming a nodule pattern, which is a typical CT finding. MRI reveals the non-mineralized areas of the hyaline cartilage with low signal intensity on T1-weighted and high intensity on T2-weighted sequences. A septal and peripheral enhancement pattern is found after application of a contrast agent [28]. Total surgical resection is the therapy of choice, as chondrosarcomas tend to be resistant to chemotherapy and radiotherapy with a high rate of recurrence after incomplete resection [29].

Chordomas are rare and slow growing low-grade tumors derived from remnants of the notochord [30]. The sacral region and the base of the skull represent the mostly affected regions. Less frequent, this tumor is localized in the cervical spine. Bone destruction, sclerosis, and intratumoral calcification are morphological signs of chordomas. Low to intermediate signal intensity on T1-weighted and high intensity on T2-weighted sequences are found in MRI. Usually chordomas show a peripheral and septal contrast enhancement. En-bloc-resection is the preferred therapy since sensitivity to chemotherapy or radiation is low [31].

Osteosarcomas accounting for 3–5 % of all spinal neoplasms are aggressive malignant tumors of mesenchymal origin. Tumor cells produce an immature matrix and osteoid. The most common sites of metastasis are the lung, bones, and liver. Risk factors for osteosarcoma are the diagnosis of Paget disease and a previous radiation therapy. In CT scans, a heterogeneous morphology caused by ossified and non-ossified areas in combination with necrosis is found. MRI is the technique of choice to evaluate the extension of the tumor into the surrounding soft tissue and neural structures. On T1- and T2-weighted images, a hypointense signal represents the mineralized parts of the neoplasm. In contrast, hyperintense signal changes in T2-weighted sequences are found in non mineralized areas with inhomogeneous enhancement of contrast agent [28]. Patients with osteosarcoma may benefit from radical resection in combination with neoadjuvant chemotherapy. Protocols for neoadjuvant chemotherapy include doxorubicin, cisplatin, high-dose methotrexate, and ifosfamide [32]. Osteosarcomas, chondrosarcomas, and chordomas are relatively insensitive to radiation, but in case of incomplete resection or as a palliative treatment, postoperative radiotherapy may be a further treatment option.

Ewing sarcoma was originally described in 1921 and is a frequent highly malignant bone tumor in adolescents and young adults. James Ewing characterized a tumor of the diaphysis of long bones which is responsive to radiation therapy. Recent results discuss a mesenchymal stem cells origin of the neoplasm [33]. Primary sites of origin are the pelvic bones and femur although the vertebra, lungs, and bone marrow of long bones are usually involved in metastatic dissemination.

A primary vertebral localization is reported with an incidence of 3.5–15 % of all cases [34]. In CT scans radiologic patterns of Ewing sarcoma are characterized by aggressive bone destruction and lysis. An extensive paraspinal soft tissue involvement is known and should be screened with MR imaging, which shows intermediate signal intensity on T1-weighted sequences and intermediate to high signal intensity on T2-weighted images [28]. The total resection of the tumor, preferably with a margin of surrounding normal tissue is the main aim of the surgical treatment. Additional neoadjuvant chemotherapy is considered as standard therapy [35, 36]. Ewing sarcoma is responsive to radiation therapy.

7.2.1.3 Solitary Plasmacytoma

Solitary plasmacytoma, which occurs in 5 % of patients with plasma cell disorders, refers to an uncommon type of plasma cell dyscrasia. The entity is caused by a localized proliferation of neoplastic monoclonal plasma cells and can be subdivided into solitary bone plasmacytomas and solitary extramedullary plasmacytomas. Solitary bone plasmacytomas affect the axial skeleton or the vertebral bodies with subsequent pathologic fractures causing spinal cord compression. Extramedullary plasmacytomas originate from soft tissue and may compress the spinal cord when they arise from the dura mater [37]. The neoplasm affects middle-aged adults (male to female ratio of 2:1) with a peak occurrence between 55 and 60 years [38]. In case of more than one affected locus or a systemic involvement, the term multiple myeloma is used. According to the guidelines on diagnosis and management of solitary plasmacytoma, the investigations should include a complete radiological staging of the skeleton as a whole, bone marrow biopsy, blood/urine tests, and MRI of the thoracic and lumbar spine [39]. MRI represents the first diagnostic choice to evaluate the osseous and extraosseous extension of plasmacytomas. In patients with a solitary bone lesion, MRI of the complete spine helps to reveal unanticipated lesions. The MR pattern is characterized by a bright signal in T2-weighted images and a hypointense signal in T1-weighted images. Postcontrast images show an enhancement of the focal lesions [40]. Radical radiotherapy is the primary treatment for patients with solitary bone plasmacytoma. Surgery may be indicated in case of structural or neurological compromise. The role of adjuvant chemotherapy is not clear, it may have a benefit in cases at high risk of treatment failure [39].

7.2.1.4 Epidural Metastases

Spinal cord compression caused by epidural metastases is a common complication affecting almost 5 % of cancer patients [41]. Approximately 10 patients per 100,000 persons per year are diagnosed with this condition [42]. Most of the metastases expand from the spine into the epidural space. In 60 % of all cases, prostate, breast, or lung cancers are the primary neoplasms followed by non-Hodgkin lymphoma, renal cell cancer, and multiple myeloma, which represent 5–10 % of all cases; colorectal cancers and metastases of sarcomas are less common [41]. It is known that carcinoma of the lung, cancer of unknown primary origin, and hematologic neoplasms manifest in 20 % initially as spinal epidural metastases [43].

Increasing back pain represents an early and the most common clinical sign. Over time patients may develop radicular pain, if metastases invade or compress nerve roots. Weakness and gait dysfunction are also frequent. Sensory deficits and bowel or bladder dysfunction follow later on in the clinical course.

MR and CT imaging of the entire spine are recommended to identify additional metastases, which may cause instability of the spine or cord compression. Up to one third of patients have more than one site of spinal cord compression. Usually T1- and T2-weighted sequences (Fig. 7.2) give sufficient information to detect the tumor

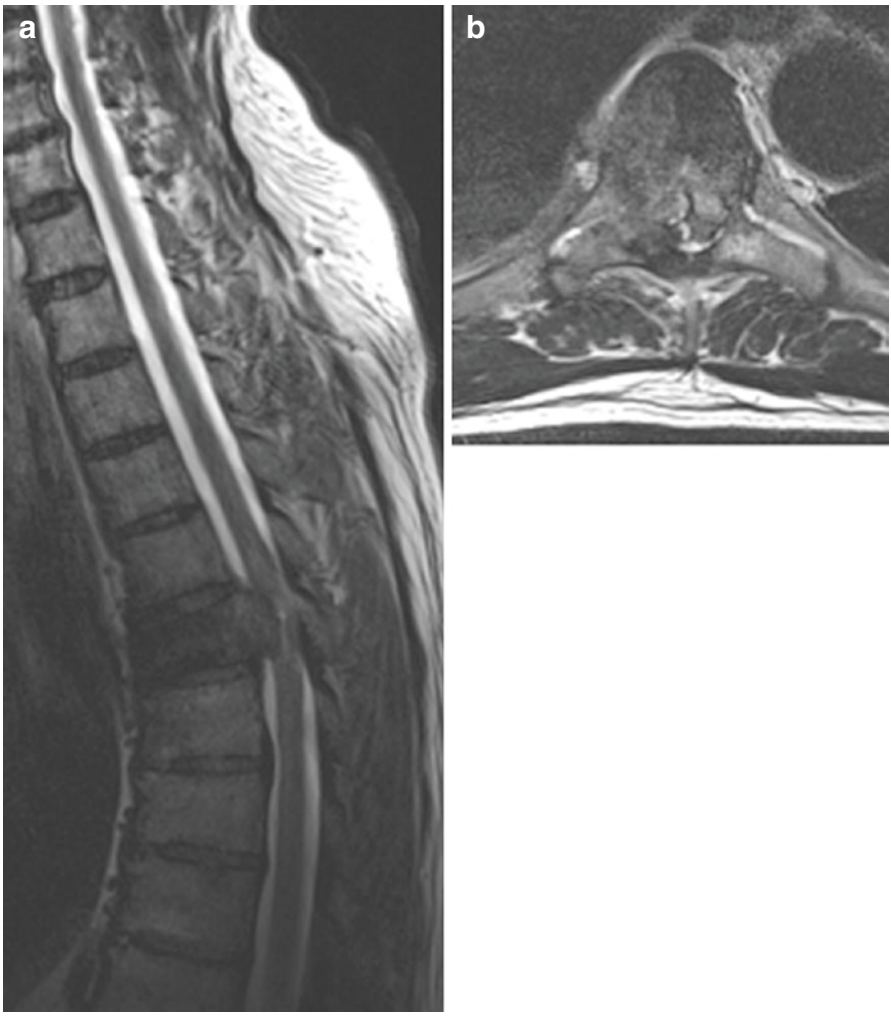

Fig. 7.2 A 74-year-old patient with primary lung carcinoma developed a paraparesis Th4 (AIS C). (**a**) In a sagittal T2-weighted MRI, osteolytic destruction of the vertebral body and a tumor mass expanding into the epidural space at level Th 6. (**b**) Ventral compression of the spinal cord. T2-weighted axial image

[44]. However postcontrast images should be routinely added. CT scans are crucial to assess bone structure and osteolytic lesions of the affected spine. Metastases of renal cell and thyroid tumors are highly vascularized lesions, which can complicate surgery with extensive bleeding. In these cases a preoperative angiography with embolization should be considered.

Decompressive laminectomy was once a treatment of choice, but metastases are often located anterior to the spinal cord. Alternative surgical strategies are developed to remove or debulk the tumor followed by subsequent spine stabilization. Radiotherapy or radiosurgery alone or in combination with chemotherapy, hormone therapy, or surgical treatment is a further treatment option for metastatic spinal cord compression [41, 45]. The so-called Tokuhashi scoring system helps to select the appropriate treatment modality based on the overall tumor-related prognosis [46, 47]. A curative treatment may be achieved with a radical en-bloc-resection of a singular metastasis. In most cases, a palliative treatment concept is realistic aiming for prevention of progressing neurological deficits, prevention of pathological fractures, and pain reduction. Early surgical decompression as opposed to delayed surgery post-48 h appears to promote superior neurological outcome in patients with metastatic spinal cord compression [48]. Cord compression due to leukemia or lymphoma-derived metastases responds to steroids, which are considered first-line treatment to provide pressure relief for the affected spinal cord [41].

7.2.2 Intradural Extramedullary Tumors and Leptomeningeal Carcinomatosis

Intradural extramedullary neoplasms are located in the subarachnoid space and represent 80 % of all intradural tumors [49].

7.2.2.1 Meningioma

Meningiomas represent benign tumors and accordingly are mostly classified as WHO grade I [50]. The slowly growing tumor arises from arachnoid cells and is usually located next to the cervical and thoracic spinal cord. The incidence is estimated about 0.3 per 100,000 persons per year. Meningiomas contribute more than 25 % of primary spinal cord tumors and are more frequent in females [51]. The occurrence of clinical signs is delayed because meningiomas grow rather slowly. Therefore, patients are asymptomatic over months or years. Local neck or back pain are common initial signs. Over time radicular pain sensory deficits, gait ataxia, and weakness as signs of a spinal cord compression may develop. MRI detects meningiomas with an isointense signal in relation to the spinal cord in T1- and T2-weighted images. Contrast agent is homogenously enhanced in the tumor. Complete surgical removal is the primary curative treatment option. In many cases a dorsal approach with laminectomy or hemilaminectomy can be performed without compromising spine stability. Recurrence rates of spinal meningioma after surgical resection have been described in the range of 1.3–15 % [52].

7.2.2.2 Schwannoma

Schwannomas originate from Schwann cells of the spinal roots with a preference for the dorsal roots. They are mostly intradurally located next to the intervertebral foramina and frequently found at cervical and lumbar level. Intramedullary location is rarely described [53]. Schwannomas are classified as WHO grade I tumors. They represent 30 % of all primary intradural and extramedullary tumors. The occurrence (0.3–0.4 cases per 100,000 persons per year) is mostly sporadic, but an association with neurofibromatosis type 2 is known [54]. In these cases, multiple manifestations are possible. Patients develop segmental pain followed by motor deficits, but clinical signs are vague in the beginning similar to meningiomas reflecting the slow tumor progression. MRI reveals typical findings, which help to differentiate these two benign spinal tumors. Besides remodeling of the adjacent bony structures in terms of expansion of the neural foramen, focal cystic changes within the benign tumor are typical for schwannomas. T1-weighted images of this tumor reveal an iso- to hyperintense signal and T2-weighted images a hyperintense signal. As described for meningiomas, complete surgical resection represents the first-line treatment. Tumor recurrence may occur several years after resection with a recurrence rate of approximately 5 % [55].

7.2.2.3 Neurofibroma

Neurofibromas are derivates from mesenchymal stem cell lines and are associated with neurofibromatosis type 1. This peripheral nerve sheet tumor is also categorized as WHO grade I and shows a fusiform shape and encloses the spinal nerve root. MR imaging shows an iso- to hypointense signal on T1-weighted sequences and hyperintensity on T2-weighted sequences. Total surgical resection is the primary treatment. Recurrence after total resection of spinal neurofibroma is rare [56].

7.2.2.4 Leptomeningeal Carcinomatosis

Leptomeningeal carcinomatosis – spreading of tumor cells in the cerebrospinal fluid – is rare in adults, but a common intradural extramedullary lesion in children, and mostly affects the lumbosacral spine with an overall poor prognosis. Lung and breast cancer, melanoma, and hematological neoplasms represent common non-CNS tumors causing leptomeningeal carcinomatosis. Primary CNS tumors such as glioblastoma, gliosarcoma, and ependymoma can also cause leptomeningeal dissemination. Patients develop multifocal neurological signs reflecting radiculopathy or myelopathy. Leptomeningeal carcinomatosis is confirmed after detection of tumor cells in the cerebrospinal fluid (CSF). However, in 10–15 % of patients, the cytology is negative [57]. MRI typically shows nodular dural contrast enhancement along the spinal cord and spinal nerve roots. Therapeutic options should be carefully balanced against the patient's clinical condition, systemic disease status, and individual preferences. Often patients are treated with a combination of radiation therapy to sites of bulky or symptomatic disease, systemic chemotherapy, and intrathecal chemotherapy. Methotrexate, thiotepa, cytarabine, liposomal cytarabine, topotecan, and etoposide represent standard chemotherapy drugs for treatment of neoplastic meningitis [57].

7.2.3 Intramedullary Spinal Cord Tumors

Only 20 % of all intradural tumors are located inside the spinal cord parenchyma (intramedullary location) [49].

7.2.3.1 Ependymoma

The most frequent intramedullary tumors are ependymomas with 60–70 % of all intramedullary neoplasms and occurring in approximately 0.21 cases per 100,000 persons per year [51]. Ependymomas belong to neuroepithelial tumors and originate from ependymal cells within the CNS. According to the WHO classification [50], four different subtypes can be distinguished: subependymoma (WHO grade I), myxopapillary ependymoma (WHO grade I), cellular ependymoma (WHO grade II), and anaplastic ependymoma (WHO grade III). Subependymomas mostly grow in the fourth ventricle followed by the lateral ventricles and are not common in the spinal cord [58]. Anaplastic ependymomas which develop more rapidly are rare and have a poor prognosis. Myxopapillary ependymomas arising from the filum terminale are located extramedullary in the lumbar cistern. The cellular ependymoma (WHO grade II) represents the most common type and is histologically characterized by ependymal rosettes and perivascular pseudorosettes. Spinal ependymomas can be associated with neurofibromatosis type 2 and are most commonly located in the cervical, cervicothoracic, and thoracic spinal cord and show a typical cystic enlargement over three to four vertebral bodies. Frequently syrinx formation is located at the interface between tumor and spinal cord [59].

Back or neck pain is typically the first clinical sign followed by sensorimotor deficits and bladder/bowel dysfunction; however, radicular and central neuropathic pain has been described. Myxopapillary ependymomas often cause compression of conus or cauda equina due to the location in the lumbar cistern.

MRI shows frequently a mostly centrally located fusiform structure over multiple vertebral segments with hypointense T1-signal and hyperintense T2-signal changes. Usually ependymomas show a diffuse heterogeneous contrast enhancement, which is not present in all subtypes (Fig. 7.3). In subependymomas (WHO grade I), contrast enhancement is weak or completely absent [60].

Evoked potential-guided microsurgical total resection is recommended and represents a curative treatment option in the majority of patients [61–63]. Leptomeningeal spread of ependymoma cells is uncommon. Cytologic examination of CSF remains clinically useful, when dissemination is suspected [64]. Surgical treatment is considered the first-line therapy. Whenever possible, a maximal resection is recommended. After resection of an ependymoma WHO grade II, MRI should be followed within 72 h to detect tumor residues. In case of a known or suspected residual lesion, postoperative radiation therapy should be considered to avoid a tumor relapse. After surgery of an ependymoma WHO grade III, radiotherapy should be performed in any case. At this point there is no known added value for additional chemotherapy. In case of tumor dissemination into the CSF craniospinal irradiation as a palliative concept should be considered. Adjuvant chemotherapy is available, which may be a

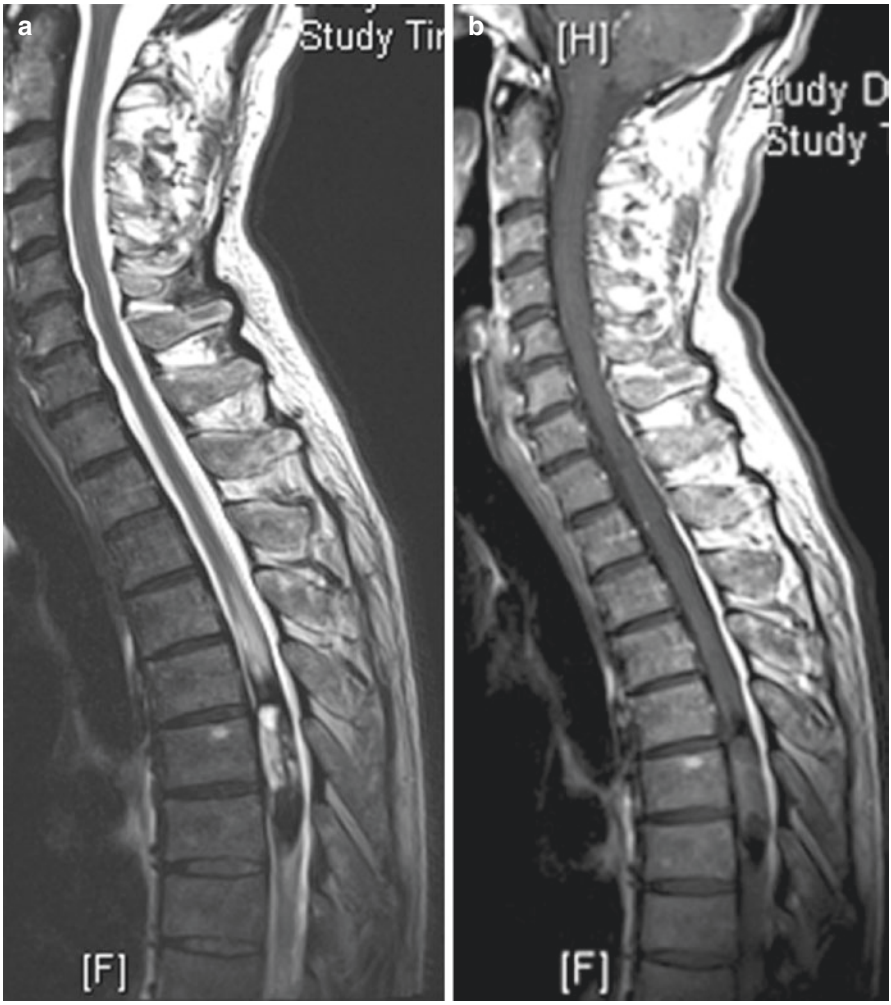

Fig. 7.3 A 57-year-old patient with paraparesis Th5 (AIS D). (**a**) Ependymoma (WHO grade II) at level Th6 extending over multiple spinal cord segments. T2-weighted image shows hyperintense signal change rostral and caudal to the tumor suggesting edema. (**b**) Contrast-enhanced T1-weighted image reveals the well-defined tumor border

treatment option for patients with recurrent malignancy. Long-term follow-up is recommended for all patients with ependymomas [65].

7.2.3.2 Astrocytoma

Astrocytomas belong to the group of gliomas and are of neuroepithelial origin, but only 3 % are located in the spinal cord. In adults they represent the second most common intramedullary malignancy (30 %) and occur in approximately 0.03 cases per 100,000 persons per year [51]. Astrocytomas are predominantly found in the

cervical spinal cord and extend over multiple segmental levels and can be associated with syrinx formation [59]. Based on the histological pattern, astrocytomas can be distinguished in pilocytic astrocytoma (WHO grad I), diffuse astrocytoma (WHO grad II), anaplastic astrocytoma (WHO grade III), and glioblastoma (WHO grade IV) [50]. In adults high-grade tumors are more common. Astrocytomas can be associated with neurofibromatosis type 1.

MRI shows a heterogenous tumor morphology with cystic formations and inconsistent contrast enhancement with an eccentric location of the lesion in the spinal cord (Fig. 7.4).

Only in pilocytic astrocytomas total resection may be attempted. In most cases, a total resection via microsurgery is not possible because a clear border between the intact spinal cord and diffuse astrocytoma, anaplastic astrocytoma, and glioblastoma

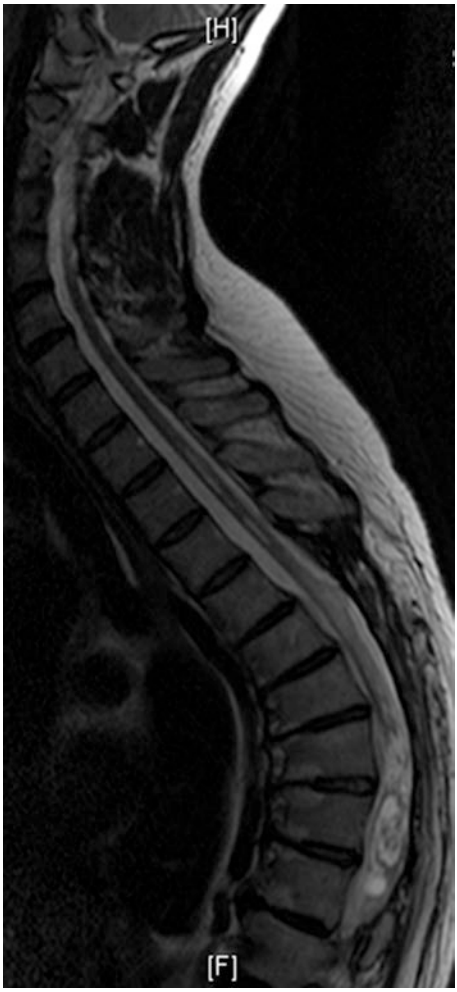

Fig. 7.4 A 41-year-old patient with paraparesis Th2 (AIS D) caused by an astrocytoma (WHO grade II) in the thoracic spinal cord. Sagittal T2-weighted image shows heterogenous signal changes and cyst formation rostral to the solid tumor

is absent. However maximal resection is recommended in patients with neurological deficits or tumor progression. In case of WHO grade II astrocytoma after complete resection, radiotherapy may be deferred until clinical or radiological disease progression occurs. Postsurgical radiation therapy should follow after incomplete resection. Additional chemotherapy should not be routinely administered. When disease progression occurs, repeated surgical resection followed by radiation therapy represents a standard treatment regimen. Chemotherapy with temozolomide is a treatment option in patients with a combined chromosome 1p/19q loss of heterozygosity in the state of progressive disease [66]. In patients with anaplastic astrocytomas, postoperative radiotherapy should be administered, and participation in clinical trials with postoperative adjuvant chemotherapy should be considered. Combination of radiotherapy with temozolomide is a further treatment option. Particularly for patients that harbor a combined chromosome 1p/19q loss of heterozygosity, treatment with temozolomide should be considered [66, 67]. In the future, stereotactic radiosurgery may play a role in the management of high-grade lesions.

7.2.3.3 Hemangioblastoma

Hemangioblastoma are rare benign highly vascularized neoplasms (WHO grade I) mostly located in the cerebellum (80 %) but can also be found in the spinal cord (20 %), predominantly in the dorsal part of the cervical or thoracic segments. They represent 2 % of all intramedullary tumors and are the third most common intramedullary lesion after ependymomas and astrocytomas occurring in 0.02 cases per 100,000 persons per year. Cyst formation is commonly seen. If associated with von Hippel–Lindau syndrome, multiple manifestations can be observed [68], which require repeated MRI follow-ups. Histologically, hemangioblastomas show a compact capillary network consisting of stromal cells, pericytes, and endothelial cells [69] with a well-defined border to the intact spinal cord. Pain and sensory deficits are common complaints. Because of the dorsal location in the spinal cord, a slowly progressing impairment of proprioception is described. The tumor usually appears as a nodule. However, it can also expand diffusely into the spinal cord. Homogenous contrast enhancement of the nodular structures is typically seen due to the intense vascularization. On T1-weighted images iso- to hypointense and on T2-weighted images iso- to hyperintense signal changes – the latter reflecting cyst or syrinx formation – are common [54]. Treatment of choice is to completely resect the well-demarcated tumor. Spinal angiography in combination with endovascular embolization may be considered before surgery to reveal the nidus with prominent dilated arteries and draining veins in order to reduce intraoperative uncontrolled bleeding.

7.2.3.4 Intramedullary Spinal Cord Metastasis

Metastases within the spinal cord parenchyma are rare and less frequent (5 % of all spinal metastases) compared to leptomeningeal metastases. Only 1–3 % of all intramedullary neoplasms are caused by intramedullary metastases. Most frequently spinal cord metastases are derived from lung cancer (50 %) followed by breast cancer with 16 %. Less frequently, melanoma, renal cell cancer, colorectal cancer,

lymphoma, and CNS tumors cause intramedullary metastases [70]. A clear preference of a certain spinal cord segment is not described. Pain and sensory deficits followed by weakness and bowel and bladder dysfunction are typically clinical manifestations. Multilocular manifestation in some instances requires complete spinal cord and brain MRI workup. Typically, hyperintense signal changes on T2- and T1-weighted images with contrast enhancement are observed within the spinal cord parenchyma. CSF analysis is rarely indicating meningeosis. The treatment strategy should be individualized based on the type and stage of the primary cancer. Radiotherapy in combination with steroids is commonly applied in radiosensitive lesions such as metastases derived from breast cancer or small cell lung carcinoma as a palliative concept [71, 72]. Chemotherapy may be an option in chemosensitive tumors mostly in combination with radiation or surgery. Only in selected cases, subtotal resection in order to preserve neurological function may be a treatment option. Overall prognosis of patients with intramedullary metastases is poor. The median survival from the time of diagnosis is less than 1 year [70, 73, 74].

7.3 Spinal Hematoma

The exact incidence of spinal hematoma is not known but appears to be low. Frequently a spinal hematoma becomes apparent with a sudden onset of clinical signs requiring urgent diagnostic evaluation and immediate surgical spinal cord decompression in case of relevant neurological deficits. Most commonly, an epidural location (about 75 % of all spinal hematomas), followed by subarachnoid (16 %) and subdural manifestation (4 %), is observed. In less than 1 %, the hemorrhage occurs within the spinal cord parenchyma. Spinal hematomas overall peak between 15 and 20 years and between 45 and 75 years of age. A similar age distribution is found for epidural hematomas, whereas subarachnoid hematoma occurs predominantly between 15 and 20 years of age [75].

7.3.1 Spinal Epidural Hematoma

In the majority of patients, the etiology of the spinal hematoma cannot be determined (40–50 %) [76]. Epidural hematomas without adequate trauma are classified as spontaneous spinal epidural hematoma. Spontaneous spinal hematomas can be associated with a trivial trauma, coughing, defecation, or a prolonged Valsalva maneuver [77] leading to a rupture of the internal vertebral venous plexus [78]. The incidence of spontaneous spinal hematomas is estimated at 0.1 cases per 100,000 persons per year [79]. Alternatively, spinal epidural hematomas can be associated with anticoagulants, platelet aggregation inhibitors or non-drug-induced coagulopathies [80–82], epidural tumors, and underlying spinal vascular malformations [83, 84]. Respective hematomas are predominantly located around the level C6 or T12 [85]. Trauma-associated spinal hematomas occur less frequently and are often associated with degenerative spine disease in the elderly patient [86]. Furthermore a spinal hematoma can be a complication of an invasive medical procedure. The

incidence of epidural hematoma in the course of spine surgery is estimated to be less than 1 % [87]. A spinal hematoma can occur as a complication of spinal anesthesia.

Injections of a local anesthetic into the subarachnoid space (spinal anesthesia) and epidural space (epidural anesthesia) represent well-established procedures. The incidence of spinal hematoma due to spinal anesthesia has been reported between 1:480,000 and 1:750,000, whereas epidural anesthesia causes spinal hematoma in 1:10,300–1:26,400 [88, 89]. As expected, concomitant oral anticoagulants or low-molecular-weight heparins increase the risk for a spinal hematoma. Concomitant application of acetylsalicylic acid and other nonsteroidal anti-inflammatory drugs further enhance the risk of a spinal hematoma [90].

Typically, patients present with acute onset neck or back pain radiating to the corresponding dermatome followed by signs and symptoms of spinal cord and/or nerve root compression. Acute hemiparesis as initial manifestation of spinal epidural hematoma is not uncommon. Therefore, patients with acute hemiparesis have to be carefully examined for signs of Brown-Sequard syndrome (dissociated sensory dysfunction; see chapter 3) to distinguish them from an acute ischemic cerebrovascular event [91]. Sometimes patients can present with subacutely progressive or remitting-relapsing neurological symptoms; sometimes the chief complaint is centered around persistent neck or back pain with relatively minor neurological symptoms. Once suspected appropriate diagnostic workup – in particular MRI – has to be performed immediately. Typically, dorsal convex lens-shaped structures can be observed as iso- to hyperintense signals on T1-weighted images and hyperintense signals on T2-weighted images (Fig. 7.5). Respective findings may extend over multiple spinal levels [92].

Immediate decompression laminectomy followed by surgical removal of the hematoma represents the first-line therapy. The preoperative severity of neurological dysfunction and the interval between disease onset and decompression surgery determine the postoperative outcome [93, 94]. Sensorimotor-complete patients show superior recovery, if decompression is performed within 36 h. A favorable outcome in sensorimotor-incomplete patients is observed, when decompression occurs within 48 h after injury [93]. Eighty-nine percent of patients with incomplete deficits show substantial recovery within 1 year, whereas only 37 % of those with a complete sensorimotor dysfunction improve [95]. In patients with mild, rapidly, and spontaneously recovering neurological deficits, surgical decompression can be postponed or even omitted. As always the perioperative risk should be weighed carefully against the clinical benefit for the patient [85].

7.3.2 Spinal Subdural Hematoma

In 1912 the first report about a spinal subdural hemorrhage was published [96]. Nowadays MRI greatly facilitates the appropriate diagnosis. Overall, a variety of predisposing factors and etiologies have been identified for this rare disease condition. Spinal subdural hematoma can be caused by iatrogenic procedures such as lumbar puncture, spinal anesthesia, or anticoagulation therapy. Vascularized spinal

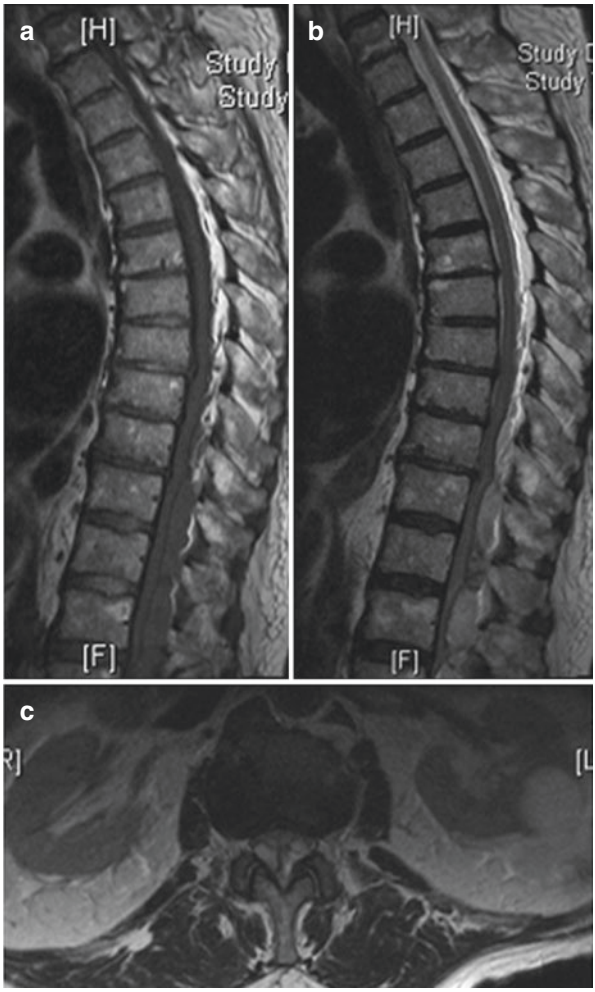

Fig. 7.5 (**a**) Sagittal T1- and (**b**) T2-weighted MRI displays an epidural hematoma extending over multiple levels of the thoracic and lumbar spine with a convex appearance compressing the dorsal spinal cord in an 84-year-old patient with paraparesis Th1 (AIS A). (**c**) Absolute narrowing of the spinal canal due to the epidural hematoma. Axial T2-weighted image

tumors, vascular malformations, or coagulation disorders can also lead to a spinal subdural hematoma. A spontaneous idiopathic acute spinal subdural hematoma is extremely rare. Suddenly increased intra-abdominal or intrathoracic pressure (e.g., by coughing or straining) can cause a rupture of radiculomedullary vessels in the subarachnoid space with a subsequent break through the thin arachnoid into the subdural space [97, 98].

Clinical signs and symptoms are similar to epidural spinal hemorrhage. Patients initially describe acute onset back pain sometimes in combination with radicular pain, especially in lumbosacral hematoma. Depending on the extent of the hemorrhage, neurological deficits will follow immediately or delayed. Headaches and

signs of meningeal irritation are also described and can indicate hemorrhage into the subarachnoid compartment.

MRI is the diagnostic of choice to visualize the hematoma, its location in relation to the meninges, and its cranio-caudal extension. Furthermore, an underlying tumor or an arteriovenous malformation can be detected. Typically a subdural hematoma is characterized by an eccentric, multilocular, or inhomogeneous multisegmental formation compressing the spinal cord (Fig. 7.6). An acute spinal subdural hematoma shows a hypo- or isointense signal in T1-weighted images and a hypointense

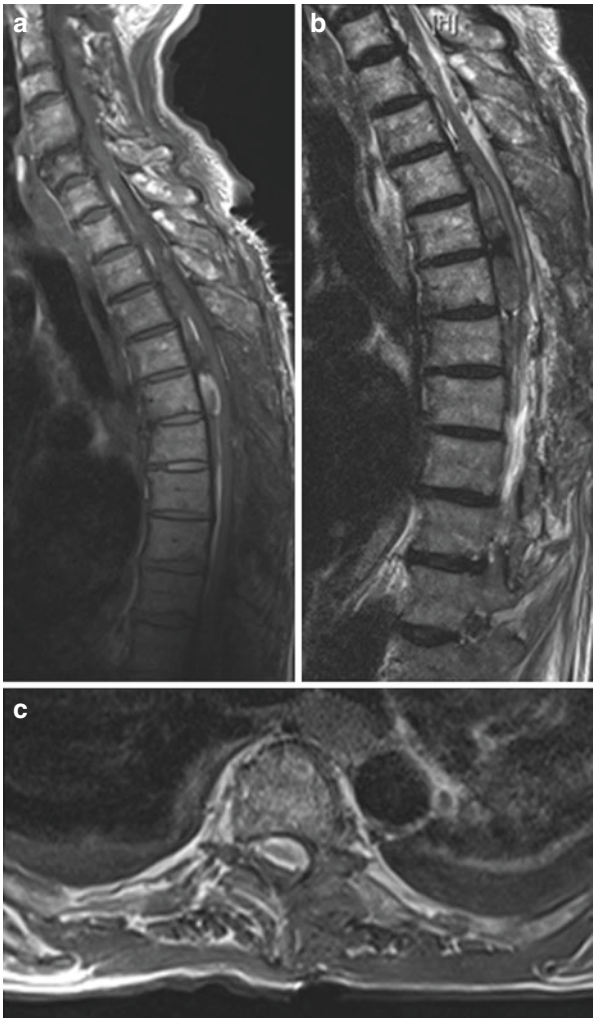

Fig. 7.6 Subacute subdural hematoma anterior to the thoracic spinal cord with a typical hyperintense signal of an inhomogeneous multisegmental formation in an 86-year-old patient with paraparesis Th10 (AIS D). (**a**) Sagittal T1- and (**c**) axial -weighted image. (**b**) Sagittal T2-weighted image showing a mass with a hypo- to isointense signal causing spinal cord compression

signal in T2-weighted images. In the subacute stage (4–7 days), hyperintensity in T1- and T2-weighted images is observed [99]. Contrast enhancement at the margin of the hematoma can be found. Spinal angiography should be performed to detect spinal artery aneurysms or arteriovenous malformations that can cause spinal subarachnoid hemorrhage [100].

Surgical decompression and evacuation remains the treatment of choice in patients with severe sensorimotor deficits, especially in cervical and thoracic locations [101]. Conservative treatment should be considered in patients presenting with back pain only and early rapid improvement of neurological deficits. In extensive dorsally located hematomas, a percutaneous drainage can be considered [98].

7.4 Cord Compression by Infectious Lesions

7.4.1 Spinal Epidural Abscess

A spinal epidural abscess – mostly based on a bacterial infection – is characterized by a collection of pus within the spinal canal outside the dura. In rare instances, fungal infections underlie a spinal epidural abscess. This disease entity has been reported with an estimated incidence at 1.8 cases per 100,000 persons per year [102]. Continuous expansion from a neighboring spondylitis, spondylodiscitis is found in half of non-iatrogenic abscesses. Pneumonias, abscesses of the retroperitoneal abscess formation, and furuncles can also cause an epidural abscess through a local transfer. Endocarditis, injections or infusion therapy, or skin abscesses can cause an epidural abscess through hematogenous dissemination. Facet infiltrations, epidural analgesia, and spinal instrumentation have been described as iatrogenic causes. Not infrequently, the original focus of the infection cannot be identified. Immunosuppression, diabetes mellitus, trauma, intravenous drug abuse, and alcoholism represent risk factors for this disease entity [103]. *Staphylococcus aureus* and *Escherichia coli* are listed the most common underlying germs [102].

Usually clinical signs develop with a latency of weeks after the primary infection. Severe back pain in combination with fever is followed by radicular signs and signs of spinal cord/cauda equina compression including bladder/bowel dysfunction.

Contrast-enhanced T1-weighted sequences show ringlike or a homogenous contrast enhancement (Fig. 7.7). Leukocyte counts and C-reactive protein indicate the activity of the infection. Blood cultures and microbial samples are required to identify the causative microorganism.

Once significant neurological dysfunction (paresis, bladder dysfunction) is observed, surgical decompression with abscess evacuation needs to be performed immediately followed by subsequent antibiotic treatment. In case of predominant pain without relevant neurological deficits, a conservative management with specific antibiotic treatment is justified [104]. Besides laminectomy also single- or multilevel interlaminar fenestration and minimal invasive techniques via a tubular retractor system for drainage are performed [105, 106]. Spinal instrumentation is performed in

case of spine instability, but the susceptibility for biofilm formation asks for a careful decision. Before a specific germ is identified, empirical antibiotic treatment with a cephalosporin is recommended based on the high prevalence of *S. aureus*-related infections. In case of spinal instrumentation, transient combination with rifampicin is recommended to avoid biofilm formation. In case of a conservative treatment regimen, a CT-guided needle aspiration should be performed for germ isolation.

7.4.2 Spinal Subdural Abscess

A bacterial infection of the subdural space between the dura and arachnoid is rare. Nevertheless the infection can extend over multiple spinal segments and provoke a

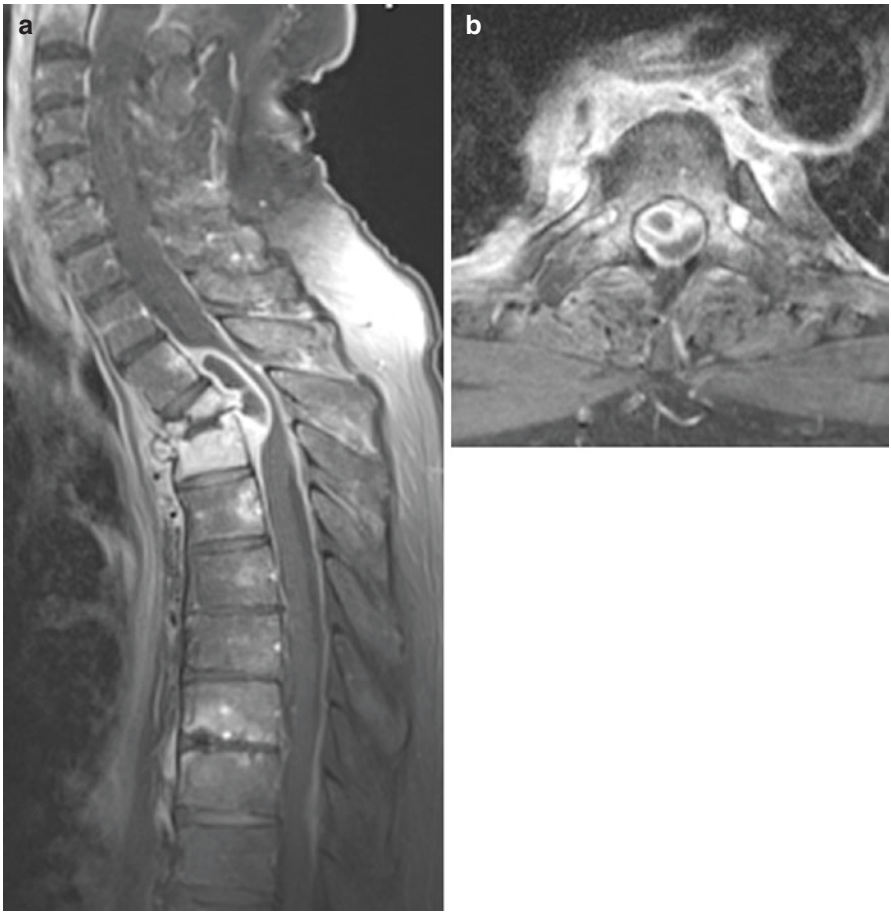

Fig. 7.7 Spondylodiscitis with consecutive epidural abscess compressing the thoracic spinal cord at level Th3 in a 62-year-old patient with paraparesis Th3 (AIS D). (**a**) Contrast-enhanced T1-weighted image displays a typical ringlike enhancement around the abscess. (**b**) Compression of the spinal cord by the abscess. Contrast-enhanced T1-weighted axial image

life-threatening infection of the CNS mostly caused by iatrogenic inoculation, trauma, or local sources. *S. aureus* and *Streptococci* represent the most frequent causative microorganisms. Patients develop rapidly fever, back pain, neck stiffness, cord compression syndrome, or signs of increased intracranial pressure. MRI reveals a subdural thickening on T2-weighted sequences and a diffuse subdural contrast enhancement. Due to the mostly rapidly progressing clinical course, immediate surgical consolidation in parallel with antibiotic and steroid treatment is warranted.

7.4.3 Pott's Spine

Spinal tuberculosis, also known as Pott's disease, is rare in developed countries but is more frequently in less developed countries where tuberculosis is endemic. In the WHO European region which comprises 53 member states and a population of around 900 million including east European countries like Georgia, Uzbekistan, Tajikistan, Kazakhstan, and Azerbaijan, an extrapulmonary manifestation is found in 17 % of all tuberculosis cases [107]. Approximately 10 % of patients with extrapulmonary tuberculosis have skeletal manifestation with a predilection for the spine [108]. Spinal manifestation is caused by hematogenous dissemination of *Mycobacterium tuberculosis* from a pulmonary or other extraosseous focus. Risk factors for spinal tuberculosis are HIV infection, drug abuse, and other immunosuppressive conditions. Particularly in Africa or Southeast Asia, a high prevalence of HIV infection exists. HIV patients have a more than 20-times higher risk to develop tuberculosis [108]. Starting as a vertebral lesion, tuberculosis can spread to the paravertebral, prevertebral, or epidural space causing abscess formation with consecutive spinal cord compression. Predominantly, the thoracic and lumbar spines are affected.

Onset of clinical symptoms is delayed and disease progression usually slow. General symptoms such as weight loss, evening rise of temperature, and night sweats are followed by more specific symptoms such as back pain, sensory deficits, paraparesis, and bowel and bladder dysfunction. In case of affection of the cervical spine, tetraparesis and involvement of cranial nerves and the brainstem are observed. The diagnosis is made based on the clinical course in combination with lab and imaging findings (CT, MRI). Intradermal tuberculin test and detection of the mycobacterium in microbial samples of the affected areas via culture, PCR, or Enzyme Linked Immunosorbent Assay (ELISA) confirm the infection. Furthermore, histological examinations of tissue samples are recommended, which typically reveal epithelioid and giant-cell granuloma. Spine CT allows to detect vertebral destruction, paraspinal calcifications, and numerous small bone fragments, which are typically found in Pott's disease. MRI is important to evaluate the extension into the soft tissue and is the best modality to localize prevertebral, paravertebral, or epidural masses [109].

Tuberculostatic drugs represent the first line of therapy. In case of spinal cord or nerve root compression, extensive abscesses, marked anterior column osteolysis with kyphosis, and instability, an additional surgical treatment is required [110]. Medical treatment is challenging and requires a close monitoring. The

collaboration with experts in infectious diseases is mandatory to prevent the emergence of multiresistant strains. According to the WHO recommendation [111], spinal manifestation of tuberculosis with neurological dysfunction should be treated with the same tuberculostatic agents, e.g., isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin, which are administered in pulmonary tuberculosis. However, an extended administration period of 6 months is recommended. In cases of tuberculosis meningitis, streptomycin should be applied instead of ethambutol. In patients with spinal cord compression, relevant abscess formation, lack of response to medical treatment, and spinal instability due to osteolysis with kyphosis, surgical treatment may be required, which includes decompression, debridement or corporectomy, and in case of instability an instrumented fusion of the spine [110]. The benefit of surgery in less severe cases is discussed controversially [108].

7.5 Cystic Lesions and Other Etiologies

Cystic lesions within the spinal canal are classified based on their anatomical localization. Epidural meningeal cysts are distinguished from intradural cystic lesions, namely, arachnoid, epidermoid, perineural, and other types of intraspinal cysts.

7.5.1 Meningeal Cysts

Spinal extradural meningeal cysts are rare. Less than 3 % of all primary spinal space-occupying lesions are caused by extradural meningeal cysts [112]. Three categories are distinguished [113]: type I, extradural meningeal cysts without containing nerve roots; type II, extradural meningeal cysts containing nerve roots; and type III, intradural meningeal cysts. A type III lesion represents an intradural arachnoid cyst. Type I cysts are subdivided into a type IA (extradural arachnoid cyst) and a type IB cyst (a sacral meningocele or occult sacral meningocele). Most frequently spinal extradural meningeal cysts are located in the thoracic spine (65 %); less frequently they are described in the lumbar (13 %), sacral spine (6.6 %), and the cervical spine (3.3 %) [114].

Clinical symptoms associated with meningeal cysts are related to cord or nerve root compression. Irritation of the adjacent periosteum and joint capsules may cause local pain, whereas rarely occurring radicular pain is related to root compression by a space-occupying cyst. Usually patients develop progressive spastic or flaccid para- or tetraparesis. Sensory deficits are less common. Sacral cysts may lead to predominant bowel or bladder dysfunction. Initially mild but intractable back pain is followed by additional neurological symptoms over months or years. In most patients, the symptoms progress in severity over time. In one third of the patients, intermittent periods of symptom remission are described [115]. Only in rare cases, remission lasts for years [116].

T2-weighted images reveal a hyperintense signal inside the cyst surrounded by a well-demarcated border without contrast enhancement, which may be found next to a spinal root [117].

Asymptomatic cystic lesions do not require treatment. Large cysts with consecutive compression of neural structures and associated clinical symptoms should be treated [118]. If total excision of the cyst cannot be accomplished due to adhesions, resection of the posterior cyst wall is the treatment of choice. Alternative surgical procedures include osseous decompression; cyst incision, drainage; marsupialization of the cyst; obliteration of the cyst–dural sac communication; lumboperitoneal, cyst–arachnoid, or ventriculoperitoneal CSF shunt surgery; and minimally invasive endoscopic treatment [112].

7.5.2 Arachnoid Cysts

Arachnoid cysts are uncommon and frequently asymptomatic incidental findings. Most frequently arachnoid cysts are found in the extradural compartment. They originate from a herniation of the arachnoid mater caused by insufficient dural tissue. In contrast, extremely rare intradural arachnoid cysts are based on alterations of the arachnoid trabeculae. The pathogenesis of these lesions is still unclear, and several etiologies, such as congenital anomalies and posttraumatic or inflammatory causes, are discussed [119].

Often symptoms are variable and nonspecific, but a spinal arachnoid cyst that compresses the spinal cord typically causes back pain and progressive spasticity or flaccid paraparesis depending on the rostrocaudal location of the cyst. Furthermore an arachnoid cyst can also present with signs of a radiculopathy.

Contrast-enhanced MRI helps to differentiate between benign cystic lesions, solid tumors, and infectious masses (abscess formation) [120]. Arachnoid cysts appear typically as hypointense on T1-weighted images and hyperintense on T2-weighted images with no contrast enhancement and no perilesional edema [121].

Surgery is not recommended for incidental spinal arachnoid cysts. Symptomatic isolated spinal arachnoid cysts should be surgically resected [122]. Whenever complete resection is not feasible, a fenestration of the cyst wall, percutaneous drainage, and shunting of the cyst into the peritoneal cavity can be therapeutic options to alleviate symptoms [123].

7.5.3 Spinal Epidermoid Cysts

Epidermoid cysts are extremely rare within the spinal canal and commonly located intracranially. Typically the cyst is slowly progressing. Epidermoid cysts can be located extradurally, intradurally/extramedullary, or intramedullary [124]. A congenital origin is related to irregular invagination of the ectoderm when the neural canal is closed during week 3–5 of the embryonic stage. In these patients the spinal epidermoid cyst exists from birth and proliferates very slowly in most cases without neurological symptoms until adolescence or adulthood. Cystic contents can calcify, which may cause neurological symptoms due to inflammatory response like an encephalomeningitis.

Muscular weakness, radiating pain, or back pain are common symptoms caused by symptomatic spinal epidermoid cysts. Mostly symptoms are caused by meningoencephalitis due to leakage from the cyst and/or of inflammatory mechanisms. Acute paraparesis due to rupture of a spinal epidermoid cyst is rarely described [125].

Epidermoid cysts show inhomogenous signal changes with MRI depending on the content of the cyst. Usually, the cyst is hypointense in T1-weighted images and hyperintense in T2-weighted images.

Surgical excision is recommended for lesions with progression of neurological symptoms associated with relevant compression of neural structures. A complete resection is usually difficult to achieve because its capsule adheres to the spinal cord and/or nerve roots [124, 126].

7.5.4 Other Types of Intraspinal Cysts

Several other types of intraspinal cysts with different origin are known: perineural cysts developing from the myelin sheath, synovial cysts originating from the facet joint caused by mucoid degeneration of the connective tissues due to repetitive dynamic loads exerted on the facet joint capsule or the posterior longitudinal ligament. Cysts caused by gas produced in degenerative disk disease, ligamentum flavum cysts, lumbar epidural varices, and perimembranous hematomas have been described [127].

7.5.5 Spinal Epidural Lipomatosis

This rare condition is characterized by a pathological proliferation of adipose tissue in the extradural space. The most common cause for this condition is long-term use of exogenous steroids; other secondary causes include endogenous steroid production by adrenal tumors, hypothyroidism, hyperprolactinemia, and other endocrinopathies. Spinal epidural lipomatosis has also been reported in cases of severe obesity [128].

Chronic back pain, lasting over several months to years, represents the most frequent symptom. Back pain can be followed by numbness, paresthesia, radicular symptoms, and slowly progressive paraparesis [129]. Neurogenic bowel and bladder dysfunction is rare.

A diagnostic criterion for a spinal epidural lipomatosis is the thickness of epidural adipose tissue. In this condition the adipose tissue is more than 6 mm thick in the posterior epidural space of the dorsal area with compression of the spinal cord on the sagittal MRI images compared to 3–6 mm in the normal spinal cord [130, 131]. Fatty tissue generates a bright hyperintense signal on non-contrast-enhanced T1-weighted images (Fig. 7.8) and an intermediate or hypointense signal on T2-weighted images. Axial scans in the lumbar spine show a characteristic thecal sac compression. A stellate appearance with three rays emanating from the central

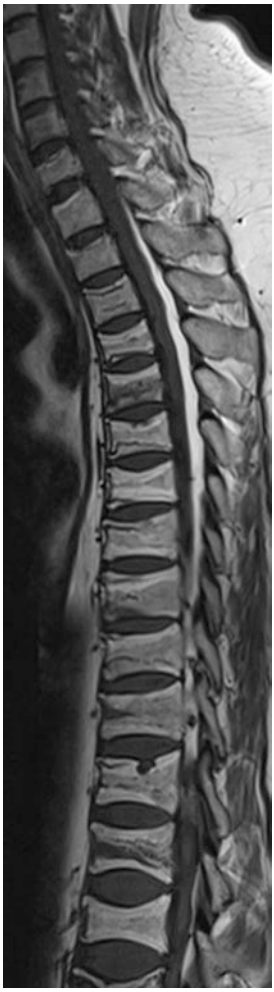

Fig. 7.8 Epidural lipomatosis causing spinal cord compression in a 28-year-old patient with paraparesis Th4 (AIS A). Sagittal T1-weighted MRI shows a longitudinally expanding hyperintense structure reflecting extensive deposition of fatty tissue

core is described. This "Y-sign" of the lumbar thecal sac has been reported to be pathognomonic for epidural lipomatosis [132].

Surgical decompression with laminectomy and resection of epidural adipose tissue is recommended in patients with progressive neurological deficits. Patients without significant signs of cord compression should be treated conservatively. Substantial weight loss and physical therapy has been reported to be successful in some cases in whom obesity is thought to be the cause of the epidural lipomatosis [133]. Endocrinological evaluation is recommended in patients without history of exogenous steroid treatment to rule out excessive endogenous steroid production. Treatment of endogenous steroid overproduction should be addressed before surgical decompression [134]. The long-term outcome is not well characterized, but recurrence after surgery is rare [133].

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Metabolic, Toxic, Hereditary, and Rare Causes of Spinal Cord Disease

8

Norbert Weidner and Zacharias Kohl

Abstract

Clinical diagnostic pathways in patients presenting with acute/subacute or chronic para- or tetraparesis routinely include imaging workup (MRI, CT, myelography) to identify spinal cord compression and cerebrospinal fluid (CSF) analysis to identify inflammatory/infectious causes of spinal cord injury. Once these diagnostic procedures have been performed without a clear hint toward the etiology of spinal cord disease, other causes have to be considered. Metabolic, toxic, hereditary (hereditary spastic paraplegia, HSP), and other rare causes, which in most instances do not present as acute onset paraparesis/tetraparesis, are likely candidates to explain the clinical phenotype. In this chapter the clinical presentation of respective entities, the specific diagnostic workup, therapy, and prognosis will be discussed. Other rare causes such as epidural lipomatosis, flexion myelopathy, and conversion (dissociative) paraplegia will be presented as well.

8.1 Introduction

The first step toward a successful identification of the specific etiology is to recognize clinical symptoms, which indicate the presence of spinal cord disease. In case a patient presents with bilateral sensorimotor dysfunction in combination with

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autonomic dysfunction (most relevant in the acute situation is neurogenic bladder dysfunction), spinal cord disease has to be considered unless it can be excluded based on additional exams such as imaging (spine CT/MRI), CSF analysis, and neurophysiology.

In case spinal cord compression can be excluded, CSF is unremarkable, and the spinal cord parenchyma does not show detectable structural changes in a properly conducted spinal MRI, diagnosis becomes more difficult. As almost always, thorough evaluation of the past medical history may give hints in respect to the correct diagnosis. In particular in cases of subacute or slowly progressive diseases, it might become particularly difficult to link the clinical presentation with a specific disease-promoting process.

Overall there appears to be a distinct "core" clinical pattern, which is typical, however not specific, for metabolic versus toxic versus hereditary causes of spinal cord disease. Of course, in each disease category, there are additional symptoms, which go beyond this "core" phenotype. In metabolic causes, which are dominated by cobalamin and copper deficiency, the dorsal columns are predominantly affected with related sensory disturbances characterized as spinal ataxia. In addition, metabolic diseases are frequently associated with polyneuropathies. Systemically incorporated toxic substances, which target specifically the spinal cord, are rare. In this category only recreational drugs are discussed, which can present clinically in a rather variable fashion. Much more uniform is the clinical picture of accidentally or intentionally intrathecally administered substances. Patients develop a mostly subacutely progressing and ascending para- and tetraplegia, which is heavily focused on the motor system, more precisely on the lower motoneuron. In addition, autonomic function is frequently affected with relative sparing of the sensory system. Finally, hereditary spinal cord disease represented by hereditary spastic paraplegia (HSP) is characterized by slowly progressive upper motoneuron degeneration with a slowly ascending spastic paraplegia. Here, the signs of autonomic and sensory dysfunction are usually mild to moderate.

8.2 Metabolic Causes

8.2.1 Subacute Combined Degeneration

8.2.1.1 Vitamin B12 (Cobalamin Deficiency)

Pathophysiology

Adenosylcobalamin is required as a cofactor for the conversion of methylmalonyl coenzyme A (CoA) to succinyl CoA. Lack of adenosylcobalamin may lead to accumulation of methylmalonyl CoA, causing a decrease in normal myelin synthesis [1]. Causes are atrophic gastritis with consecutive cobalamin malabsorption, gastric surgery, acid reduction therapy, parasitic infestation by fish tapeworm, hereditary enzymatic defect, and rarely strict vegetarianism. Often exact causes cannot be identified.

Clinical Presentation

Macrocytic anemia is the most common clinical finding. The macrocytosis may precede the anemia by months. Symptoms related to myelopathy are as follows: gait disturbance, hypesthesia, dysesthesia, impairment of vibration and position sense. Moreover, autonomic dysfunction represented by constipation, erectile dysfunction, and urinary frequency have been described. Tendon reflexes can be hyperactive with pyramidal signs; affection of the motor system presents with a typically mild para- or tetraparesis. Facultative findings are cognitive impairment/dementia [2]. Often an inverse relationship between hematologic and neurological abnormalities is observed [3].

Diagnostics

Analysis of serum cobalamin represents the most widely used screening test. However, sensitivity and specificity are poor. Serum methylmalonic acid and plasma total homocysteine (methylmalonic acid more specific, homocysteine more sensitive) are employed as ancillary tests. Serum methylmalonic acid and plasma total homocysteine are good monitoring tools and should be measured annually.

To determine the causes of cobalamin deficiency means to determine the causes of malabsorption. In this respect the so-called Schilling test is considered obsolete. Elevated serum gastrin and decreased pepsinogen have a limited specificity, whereas positive anti-intrinsic factor antibodies are more specific [3].

With spinal MRI hyperintense signal changes in the posterior and lateral columns with facultative contrast enhancement, and spinal cord atrophy can be observed [4, 5]. In some instances anterior columns show similar signal changes. Neurophysiologically, tibial nerve sensory evoked potentials (SEPs) are found frequently to be abnormal, whereas delayed P37 responses are observed in median nerve SEP. Motor evoked potentials (MEPs) are abnormal only in a subset of patients showing prolonged central motor conduction times [2]. Cobalamin deficiency can promote concomitant or even exclusive neuropathic changes in peripheral nerves. Respective nerve conduction and electromyogramm (EMG)-studies indicate an axonal polyneuropathy [6]; however, abnormal findings are not specific for cobalamin deficiency-related polyneuropathy.

Therapy

For immediate effectiveness cobalamin (1000 μg cobalamin) should be administered initially intramuscularly. Thereafter, 8–10 injections over 3 months followed by monthly injections are recommended. Since 1.2 % of any oral dose of cobalamin is absorbed unrelated to intrinsic factor, 1000 μg of oral cobalamin is also effective for substitution in cases of malabsorption. As a first treatment effect within 1 week after substitution, reticulocytosis can be detected [3]. Mean corpuscular volume (MCV) normalizes within 8 weeks after cobalamin substitution (once daily for 4 weeks, then once weekly for 1 year, then once per month) [2]. Neurological symptoms start to improve as early as 1 week and continue to improve until 3 months after cobalamin substitution. In parallel, nerve conduction velocities and median nerve SEP normalize. Signal changes in the spinal cord detected with MRI may disappear over time.

8.2.1.2 Copper Deficiency

Pathophysiology

Balanced oral food intake covers the required copper intake. Copper is absorbed in the stomach and duodenum. There, zinc and iron can inhibit copper absorption. Following uptake copper becomes transported in the bloodstream via ceruloplasmin and subsequently integrated into a variety of key enzymes such as oxidoreductases and monooxygenases. Ceruloplasmin, which has not bound copper, becomes rapidly degraded. Acquired copper deficiency (serum copper levels below 0.1 μg/ml) is typically caused by upper gastrointestinal surgery or zinc overload. Gastrointestinal surgery can be divided into non-bariatric surgery (mostly partial gastrectomy for peptic ulcer disease) and bariatric interventions (weight loss surgery) [7]. Malabsorption of copper can also be caused by celiac disease. More likely excessive zinc intake competes with copper uptake in the gut and thus reduces copper serum levels. Zinc overload is typically induced by zinc-containing denture creams [8] or zinc supplementation, e.g., to prevent or treat common colds. Rarely, a lack of appropriate intake represents the single cause of copper deficiency.

Clinical Presentation

The interval between upper gastrointestinal surgery and first symptoms ranges between 5 and 46 years. Clinical symptoms such as spastic gait and sensory ataxia related to a myelopathy or myeloneuropathy develop subacutely. Cases of combined copper and cobalamin deficiency have been described [9].

Diagnostics

Anemia, leukopenia, and ringed sideroblasts are common hematological manifestations. Similar to subacute combined degeneration, T2 MRI shows hyperintense signal changes in the dorsal and lateral columns. Besides abnormalities in SEPs, nerve conduction studies and EMG may reveal axonal loss in peripheral nerves. Serum copper and ceruloplasmin are found decreased. In case of a non-compressive myelopathy of unknown origin and related clinical symptoms, serum copper and ceruloplasmin levels should be analyzed.

Therapy

If possible, the underlying cause for copper deficiency needs to be treated. For example, excessive zinc uptake due to denture creams or oral zinc supplementation needs to be stopped. Oral supplementation of 8 mg of elemental copper per day is sufficient to restore copper storages. For obvious reasons care should be taken to avoid combinatorial preparations of copper and zinc. In case copper serum level and hematological findings do not normalize, parenteral copper substitution may be required. Neurological symptoms will improve invariably [9].

8.2.1.3 Hepatic Myelopathy

Pathophysiology

As opposed to hepatic myelopathy, hepatic encephalopathy is a well-recognized neurological disease entity, which has been linked pathophysiologically to

portacaval shunts with consecutive increase of nitrogenous products such as ammonia [10]. However, blood ammonia-lowering therapies, which are effective in hepatic encephalopathy, have not been shown to improve signs of hepatic myelopathy. Nutritional factors such as cobalamin deficiency may be relevant and, however, have not been positively confirmed as underlying cause. Structural changes, which have been obtained from postmortem analysis, include demyelination of pyramidal tracts with only occasional affection of the dorsal columns. Axonal loss is rather mild if present at all.

Clinical Presentation
Approximately 90 cases are described in the literature. Patients typically present with subacute onset of spastic paraparesis showing a slow progression over several years. Sensory and autonomous deficits are in most instances minimal. In the majority of cases, hepatic encephalopathy precedes the manifestation of myelopathy.

Diagnostics
Confirmation of myelopathy by means of ancillary exams is difficult. Imaging – in particular MRI – usually does not show any abnormalities along the spinal cord. Likewise CSF analysis does not provide any relevant clues. Therefore, the proper diagnosis can only be confirmed by excluding all relevant differential diagnosis of non-compressive spinal cord disease. Neurophysiological analysis (evoked potentials) reveals prolonged latencies or even absent motor or sensory responses, which are of course not specific for hepatic myelopathy.

Therapy
As mentioned above blood ammonia-lowering therapies do not ameliorate symptoms or the disease course of hepatic myelopathy. Single cases suggest that occlusion of a splenorenal shunt and liver transplantation promote neurological improvement in a hepatic myelopathy patient [11, 12].

8.3 Toxic Causes

8.3.1 Nitrous Oxide (N_2O)

N_2O inactivates cobalamin through irreversible oxidation of the cobalt core. Exposure to N_2O (laughing gas), which is commonly used as inhalational anesthetic agent or abused for its euphoriant properties, can lead to an acute myelopathy, typically in elderly patients with an unrecognized cobalamin deficiency [13, 14]. Myelopathy can develop already after single exposure to N_2O. Besides myelopathy neuropathies and mental status changes have been described. MRI in typical cases shows T2 signal changes in the dorsal and lateral columns [15]. Routine cobalamin and MCV testing is advised before surgical procedures involving N_2O exposure in the elderly are performed. In case of low levels, cobalamin should be substituted prophylactically.

8.3.2 Recreational Drugs (Heroin, Ecstasy, Cocaine)

Pathophysiology
Heroin and cocaine are the main recreationally used drugs, which have been described to cause myelopathy with subsequent sensorimotor and autonomous dysfunction. In case of heroin, it is still unclear which pathomechanisms are responsible for the observed myelopathy. Direct neurotoxicity, hypotension, vasculitis, and a hypersensitivity reaction have been discussed as underlying mechanisms. Hypersensitivity has been favored in some cases, since onset of disease followed a heroin abstinent period with subsequent i.v. or intranasal insufflation of heroin [16]. In another study, clinical and neurophysiological evaluation indicated selective damage to spinal ventral horn motoneurons suggesting a neurotoxic mechanism [17]. Ecstasy has been described only in a single case report, where the drug was inhaled together with heroin. Therefore, it is unknown whether ecstasy contributed at all to the observed myelopathy [17]. In terms of cocaine, ischemia is the likely underlying mechanism in cases of myelopathy paralleling the likely pathomechanism for cerebral lesions [18].

Clinical Presentation
In a number of heroin cases, symptoms developed after drug administration and a subsequent symptom-free interval of several hours. Thereafter, flaccid paraplegia with urinary retention and diminished rectal tone has been described [16, 17]. Cocaine use related to myelopathy has been reported within several hours after drug inhalation. The myelopathy is confined to the ventral portion of the cervical spinal cord presenting similar to central cord syndrome with pronounced upper extremity weakness and rather moderate involvement of the lower extremities [18]. In case of myelopathy confined to the dorsal columns, paresthesias and variable degrees of deep sensation loss may represent the only clinical signs [19]. Neurological recovery over time is variable.

Diagnostics
Depending on the clinical presentation, spinal MRI indicates the affected rostrocaudal and cross-sectional extent of the lesion. Electrophysiological workups (EMG, motor nerve conduction studies) are recommended to confirm lower motoneuron involvement.

Therapy
Besides rehabilitative interventions, no specific treatments have been described to be effective. Even in cases where hypersensitivity has been proposed as potential underlying mechanism [16], immunomodulatory therapies such as the application of steroids have not been tested.

8.3.3 Therapeutic Intrathecal Drug Administration: Cytosine Arabinoside (ara-C) and Methotrexate (MTX)

For prophylaxis and treatment of intrathecal spread of tumor disease (e.g., leukemia, glioblastoma), several cytotoxic agents are routinely administered via the intrathecal route. Thus far, cytosine arabinoside (ara-C) and methotrexate (MTX) represent the most commonly used cytotoxic agents. According to a recent review, more than 30 pediatric patients with paraplegia in the course of intrathecal chemotherapy have been reported [20].

Pathophysiology
There is sparse information regarding the mechanism underlying CNS damage due to intrathecal chemotherapy. Postmortem analysis revealed primary neuronal damage with secondary myelin breakdown and axon degeneration. In particular spinal cord areas, which are in direct contact with CSF, are at highest risk to be damaged by the cytotoxic agent [21].

Clinical Presentation
Patients typically present within hours after intrathecal injection of ara-C or MTX in a prodromal stage with signs of meningeal irritation such as headache, diffuse pain, nausea, vomiting, and fever. Within days up to several weeks, a progressive ascending weakness in the lower extremities and neurogenic bladder dysfunction follow. Sensory deficits are mostly mild if not absent [20]. In severe cases, cranial nerve palsies, visual impairment, and progressive decline of consciousness develop. In a series of 23 patients, ten patients survived with persistent paraplegia, three remained permanently respirator dependent, and eight patients died. Two patients recovered completely [22].

Diagnostics
Early radiological diagnostics including spinal MRI usually reveal unremarkable results. In some instances diffuse swelling with hyperintense signal changes in T2-weighted images can be seen. Besides elevated protein level, standard CSF analysis is normal. As a specific marker for myelin breakdown, the myelin basic protein level is elevated.

Therapy
Once patients present with a progressive paraparesis, there is no specific therapy available. Currently it has yet to be defined which patients will be at risk to develop such a complication in the course of an intrathecal chemotherapy. It appears that preceding CNS radiation therapy and combined intrathecal chemotherapy (MTX together with ara-C) represent risk factors for a respective

complication. Prophylactic treatment with concomitant steroids intrathecally, immunoglobulins, or vitamin substitution has not shown to protect against chemotherapy-induced paraplegia.

8.3.4 Diagnostic Intrathecal Drug Administration: Methylene Blue

In the past, methylene blue was routinely injected intrathecally to detect CSF leakage.

Pathophysiology
The mechanism underlying the toxic effects of methylene blue circulating in the CSF after lumbar intrathecal injection is still unknown. Postmortem analysis in a subject surviving the injection more than 10 years revealed spinal cord necrosis [23].

Clinical Presentation
A patient who received a methylene blue injection into a protruded disc at thoracic level for easier identification during spine surgery was transferred to our center. Within minutes the patient developed a rapidly progressing tetraplegia, respiratory failure, cranial nerve palsy, and hydrocephalus malresorptivus. Sensory and autonomous functions were only mildly affected. Over time he regained minimal motor function showing diffuse lower motoneuron damage.

Diagnostics
The temporal sequence of a progressive tetraplegia in the course of an intrathecal injection or an injection close to the intrathecal compartment clearly explains the etiology relevant for the clinical picture.

Therapy
There is no known therapy which may help to reduce damage to the spinal neural tissue. More than 40 years ago, clear warnings were published, which strongly disencourage intrathecal injections of methylene blue for its known above-described complications [24, 25]. Therefore, one could think that the description of methylene blue injections causing severe neurological dysfunction should be rather added to a history chapter. Unfortunately, the case description from our patient and a recent report indicating that methylene blue is still being used to identify the location of CSF leakage [26] demonstrate that methylene blue is still considered for diagnostic purposes directly in the CSF or in close proximity. Even worse, a recent randomized placebo-controlled clinical trial reported that intradiscal methylene blue injections dramatically reduce symptoms in chronic lower back pain patients [27]. Based on the above-described complications, any kind of methylene blue injection in close proximity to the nervous system is strongly disencouraged [24, 25, 28].

8.3.5 Diagnostic or Therapeutic Intrathecal Drug Administration: Spinal Anesthesia

Spinal anesthesia represents a procedure, which is applied worldwide millions of times each year and is considered to be safe. Nevertheless, numerous case reports describe the occurrence of progressive paraplegia in the course of spinal and epidural anesthesia [29].

Pathophysiology
So far it is unknown what ultimately causes the clinical picture of progressive paraplegia. It can only be speculated that either a hemorrhage in the course of the required lumbar puncture, the local anesthetic drug itself, unknown contaminants, or administered disinfectants cause the adhesive arachnoiditis, which subsequently affects the spinal cord parenchyma and nerve roots with respective neurological dysfunction. Respective factors induce a severe inflammatory reaction of the pia and arachnoidea followed by adhesion and tethering of nerve roots and spinal cord parenchyma. The blockade of CSF circulation can induce extensive syringomyelia and hydrocephalus malresorptivus.

Clinical Presentation
The interval between spinal/epidural anesthesia and presentation of neurological dysfunction varies greatly. Initial symptoms such as back pain, nausea, and headache are rather unspecific and rarely lead to confirmation of the diagnosis. More specific symptoms such as paraparesis and bladder and bowel dysfunction can appear within a few hours up to several months.

Diagnostics
Once clinical signs reflecting spinal cord disease become apparent, spinal MRI should be performed. MRI findings are characteristic for adhesive arachnoiditis showing conglomerations of adherent nerve roots residing centrally within the thecal sac, nerve roots adherent peripherally, and soft tissue masses replacing the subarachnoid space [30].

Therapy
In case of compression of neural structures (spinal cord, radices), decompressive laminectomy might be a strategy to slow down disease progression. Careful neurosurgical lysis of adherent meningeal structures can represent an additional treatment option. However, outcome following respective interventions is not favorable in most instances [31].

8.3.6 Accidental Intrathecal Drug Administration

The majority of reported cases of inadvertent intrathecal drug administration with the consequence of para- or tetraplegia are related to chemotherapeutic agents. The

most notoriously accidentally intrathecally administered drug is vincristine. Thus far, 31 cases worldwide have been reported, where vincristine was injected into the intrathecal space with a mostly fatal outcome [32]. All individuals surviving the injection suffered from severe paraparesis. Besides vincristine intrathecal injections have been reported for the chemotherapeutic agents vindesine, asparaginase, bortezomib, daunorubicin, and dactinomycin. However, the majority of related case reports describe fatal cases. None of these cases survived in the long term with para- or tetraparesis.

Pathophysiology
Vincristine has a strong affinity to tubulin and neurofilament, thus destructing the cytoskeleton of neurons. Histologically, severe degeneration of myelin and axons with pseudocystic transformation most prominently in the lumbosacral and thoracic spinal cord has been described [33].

Clinical Presentation
Within hours to few days after intrathecal injection of vincristine, patients present with rapidly progressing paraparesis, urinary retention, and loss of anal sphincter function.

Diagnostics
Once the history of accidental vincristine injection is available, no further diagnostics are required. Spinal MRI shows a perimedullar enhancement around the conus medullaris. Neurophysiological analysis reveals acute denervation of affected muscles indicating predominant damage to the lower motoneuron (ventral horn, radix).

Therapy
Only patients, where measures to dilute the drug in the cerebrospinal fluid are applied immediately, survived, however, with the consequence of severe neurological deficits. The most successful therapy seems to be the simultaneous placement of an external ventricular and a lumbar drain with consecutive craniocaudal irrigation of ringer solution. In order to enhance clearing of the drug through the infused solution, fresh frozen plasma has been added [33].

8.4 Hereditary Causes (Hereditary Spastic Paraplegia)

Neurologic syndromes, in which progressive bilateral lower extremity weakness and spasticity (each of variable degree) are the predominant manifestations and for which gene mutations are proven or assumed as the major causative factor, are designated as hereditary spastic paraplegia (HSP). First described by Adolf von Strümpell in 1880 [34], HSP constitutes a clinically and genetically heterogeneous group of neurodegenerative disorders, historically divided into “pure” and “complicated” forms [35, 36]. Many HSPs are caused by mutations in genes encoding for proteins involved in the maintenance of corticospinal tract neurons, causing distal

axonopathy of the longest corticospinal tract axons [37]. Nevertheless, HSP represents with a strong genetic heterogeneity. To date, 72 different spastic gait disease loci have been identified [38], and 54 spastic paraplegia genes (SPG) have already been cloned; other HSP causative genes are not in the SPG classification yet [39]. HSPs are transmitted in an autosomal dominant (AD), autosomal recessive (AR), X-linked (XL), or mitochondrial manner [40]. Moreover, sporadic HSP due to true de novo mutations or reduced penetrance of AD mutations as well as single cases in unrecognized AR kindred are common [41]. Due to the fact that sole clinical parameters are not reliable to differentiate the SPG subtypes, molecular testing is essential, despite the fact that around 30 % of affected patients have no genetic diagnosis [39]. The prevalence of all forms of HSP ranges from 4.1 to 9.8/100,000 [42–44]. In the European populations, AD HSP are more frequent than other forms [45], and 40–45 % of those have mutations in the SPAST gene [46]. In contrast, AR HSP are more frequent in consanguineous populations with a prevalence of up to 5.7/100,000 [42]. Mutations in KIAA1840/SPG11 represent the most common cause of AR HSP [47]. Sporadic HSP cases are frequent in clinical practice, with a prevalence of 1.3/100,000 in Norway [44]. Moreover, some of these cases could be explained by mutations in known genes, e.g., in SPG4 [39, 48].

Clinical Presentation

In most patients, HSP initially presents with progressive gait impairment due to lower extremity weakness and spasticity. Urinary urgency is common in HSP and occasionally may be an early feature. Symptoms may be first evident at any age, from early childhood through senescence. In general, subjects with pure HSP report progressive difficulty walking, often requiring canes, walkers, or wheelchairs. Besides their lower limb weakness and spasticity, they often present with diminished vibration and joint position sensation on the lower limbs [36]. The severity of spasticity and lower limb weakness varies between patients. Patients have a normal life expectancy and do not experience loss of dexterity, strength, or coordination in the upper extremities, dysarthria, dysphagia, or any other "complicating" neurological symptom. Age of onset in pure HSP is highly variable; progression of symptoms is usually slow over the years, without abrupt worsening or remissions [49].

Complicated HSP is characterized by neurological or non-neurological features in addition to the pure phenotype. Respective patients can present with spasticity in the upper extremities, cognitive impairment, epilepsy, extrapyramidal disturbances (parkinsonism, chorea, dystonia), dysphagia, dysarthria, cerebellar abnormalities (ataxia, nystagmus, tremor), spinal cord atrophy, muscle wasting, peripheral polyneuropathy, thin corpus callosum, or white matter lesions, in the absence of coexisting disorders [40]. Non-neuronal manifestations of complicated HSP include gastroesophageal reflux, orthopedic abnormalities (foot deformity, scoliosis, maxilla hypoplasia), retinopathy, macular degeneration, optic atrophy, cataract, facial dysmorphism, deafness, or skin lesions. Occasionally, complicated HSP might present with a pure phenotype in early phases of the disease, while complicating symptoms develop later on.

Importantly, marked clinical variability does not allow generalizations that apply to all HSP types and patients: Age of symptom onset ranges from infancy through late adulthood. The gait disturbance ranges from non-disabling, subtle forward-shifted heel strike to severe spastic paraplegia resulting in wheelchair dependence. Lower extremity spasticity is often but not always accompanied by weakness of the legs, primarily affecting iliopsoas, hamstring, and tibialis anterior muscles. Sometimes, symptoms begin asymmetrically, while over time both legs are more or less similarly affected. Frequent urinary bladder disturbance typically manifests as urinary urgency; defecation might be affected as well [49]. In general, there is marked clinical variability between different genetic types of HSP, as well as between individuals with the same genetic type. In addition, the course of HSP is also quite variable. Early-onset HSP may not worsen significantly over many years; adult-onset HSP can present with very slow progression over decades as well as more profound deterioration over 10–15 years. Onset and progression of symptoms over days to months is not typical for HSP and suggests alternative disorders [49].

Diagnostics

HSP can be suspected when patients present with slowly progressing spastic paraplegia of lower limbs, potential urinary urgency, and subtle sensory disturbances, usually in the context of suspicious family history. Nevertheless, several conditions need to be ruled out (Table 8.1) [49].

Diagnostic steps include individual and family history to detect the type of transmission. Moreover, a careful neurological examination, neurophysiological testing (nerve conduction studies, EMG, MEP, somatosensory evoked potential (SSEP), visual evoked potential (VEP)), imaging studies (spinal MRI, CT), and laboratory tests are needed for diagnosis, in particular to identify pure and complicated forms prior to genetic testing (Table 8.1). Screening for SPG mutations is usually carried out by direct Sanger sequencing and needs to be coupled with multiplex ligation-dependent probe amplification [39]. Recent improvements analyzing large panels of SPG genes by next-generation sequencing (NGS) permit confirmation of diagnosis in many patients; nevertheless this approach does not cover all SPG genes and may not identify all gene copy variants, including exon deletions [51]. Genetic testing is most useful to confirm a clinical diagnosis of HSP, and results of genetic testing need to be interpreted in the light of the clinical context (Table 8.2). Importantly, HSP gene variations with unknown clinical significance need careful consideration, in particular when the clinical diagnosis does not conform to HSP [49]. Genetic counseling is recommended for affected families, and the gene test results must consider mode of inheritance, and the possible degree of genetic penetrance, which is not very well known in most types of HSP [52].

Genetic counseling aims to inform affected patients and unaffected family members at risk about the nature and inheritance of the disorder. In case of AD transmission, most affected individuals have an affected parent, depending on genetic penetrance. Nevertheless, the frequency of de novo mutations causing AD HSP is unknown. In general, caution must be exercised in providing genetic counseling and prognosis for many HSP types, due to unclear genetic penetrance and insufficient

Table 8.1 Differential diagnosis of hereditary spastic paraplegia

Category	Examples	Recommended diagnostics
Structural abnormalities of the brain and spinal cord	Spinal cord compression from neoplasm or spondylosis, tethered cord syndrome, spinal cord arteriovenous malformation	MRI of entire neuraxis
Leukodystrophy	Adrenomyeloneuropathy, Krabbe disease, metachromatic leukodystrophy, vitamin B12 deficiency, mitochondrial disorders	Vitamin B12, methylmalonic acid, serum very long chain fatty acids (VLCFA), beta-galactosidase, arylsulfatase, serum lactate, and pyruvate
Chronic inflammatory disease	Multiple sclerosis (primary progressive, secondary progressive)	Cerebrospinal fluid analysis for immunoglobulin index and polyclonal bands
Infectious diseases	Tropical spastic paraplegia due to HTLV-1 infection, tertiary syphilis	HTLV-1, syphilis serology, (HIV)
Other motoneuron disorders	Amyotrophic lateral sclerosis, primary lateral sclerosis, distal hereditary motor neuropathy	Serial electromyography (for the first 2–5 years of adult-onset and progressive spastic paraparesis)
Other degenerative neurological disorders	Friedreich ataxia, spinocerebellar ataxia type 3 (SCA 3)	Friedreich ataxia and SCA3 gene analysis
Environmental toxins	Hypocupremia, lathyrism, konzo, organophosphate-induced neuropathy	Serum copper, serum zinc
Other	Spastic diplegic cerebral palsy, dopa-responsive dystonia, stiff person syndrome	Trial of low-dose levodopa (2–4 weeks)

Adapted from [50]

information about the full phenotypic spectrum. In particular, the clinical description of the majority of genetic types of HSP is limited to one or a few families (Table 8.2).

Therapy

Currently, no specific treatments to prevent, halt, or reverse the pathological processes underlying HSP are available. Treatment options are exclusively symptomatic. Spasticity is managed by regular physical therapy, occupational therapy, assistive walking devices, orthotics, or drugs reducing muscle tone, in particular baclofen or tizanidine [41]. Chemodenervation with botulinum toxin A or B can be an alternative option [53, 54], as well as intrathecal baclofen therapy in selected cases. Secondary complications, such as tendon contractures, scoliosis, or foot deformities, may be delayed or even prevented by intense and regular physical therapy. Urinary urgency can be treated with anticholinergic drugs. Pain, a quite common symptom in HSP, should be treated according to general guidelines. Neuropathic pain benefits from gabapentin and pregabalin. In complicated forms patients with cognitive decline or dementia may profit from cholinergic drugs, while epilepsy

Table 8.2 Common genetic types of HSP

SPG locus	Gene/protein	Onset	Phenotype	Additional clinical features
Autosomal dominant HSP				
SPG3A	*ATL1*/atlastin-1	EO	P or C	Ataxia, sensorimotor axonal neuropathy, intellectual disability, optic atrophy, lower limb muscle atrophy
SPG4	*SPAST*/spastin	VO	P or C	Cognitive impairment, amyotrophy of small hand muscles, epilepsy, upper limb spasticity, pes cavus
SPG6	*NIPA1*/NIPA1	EO	P or C	Idiopathic generalized epilepsy, polyneuropathy, atrophy of small hand muscles, upper limb spasticity, pes cavus
SPG8	*KIAA0196*/strumpellin	AO	P	–
SPG10	*KIF5A*/kinesin HC5A	EO	P or C	Distal muscle atrophy, cognitive decline, polyneuropathy, deafness, retinitis pigmentosa
SPG17	*BSCL2*/seipin	EO	C	Amyotrophy of hand muscles (Silver syndrome)
SPG31	*REEP1*/REEP1	EO	P or C	Peripheral neuropathy, cerebellar ataxia, tremor, dementia, amyotrophy of small hand muscles
Autosomal recessive HSP				
SPG5A	*CYP7B1*/OAH1	VO	P or C	Axonal neuropathy, WMLs, optic atrophy, cerebellar ataxia
SPG7	*PGN*/paraplegin	VO	P or C	Cerebellar atrophy, PNP, optic atrophy, TCC, axonal neuropathy *Caution*: *AD inheritance possible*!
SPG11	*KIAA1840*/spatacsin	VO	P or C	TCC, seizures, cognitive decline, upper extremity weakness, parkinsonism, dysarthria, slowly progressive familial ALS
SPG15	*ZFYVE26*/spastizin	EO	C	Pigmented maculopathy, distal amyotrophy, dysarthria, intellectual deterioration

Table 8.2 (continued)

SPG locus	Gene/protein	Onset	Phenotype	Additional clinical features
SPG20	*SPG20*/spartin	EO	C	Distal muscle wasting (Troyer syndrome), intellectual disability, dysarthria, cerebellar signs, WMLs
SPG23	Unknown	EO	C	Pigmentary abnormalities, cognitive impairment, facial and skeletal dysmorphism
SPG46	*GBA2*/GBA2	EO	C	Dementia, cataract, cerebellar atrophy, TCC, hypogonadism in males
SPG54	*DDHD2*/DDHD2	EO	C	Dysarthria, cognitive decline, TCC, WMLs, dysarthria, strabismus
SPG56	*CYP2U1*/CYP2U1	EO	P or C	Dystonia, WMLs, cognitive impairment, TCC, axonal neuropathy, basal ganglia calcifications
X-linked HSP				
SPG1	*LICAM1*/NCAM	EO	C	Cognitive impairment, adducted thumbs, aphasia
SPG2	*PLP1*/MPLP	EO	P or C	Cognitive impairment, polyneuropathy, nystagmus, seizures
SPG22	*SLC16A2*/MCT8	EO	C	Neck muscle hypotonia in infancy, cognitive impairment, distal muscle wasting, ataxia, dysarthria, abnormal facies
Maternal (mitochondrial) inheritance HSP				
ATPase6 gene	Mitochondrial ATP6	AO	C	Axonal neuropathy, cardiomyopathy, cerebellar syndrome

EO early onset, *VO* variable onset, *AO* adult onset, *P* pure, *C* complicated, *WML* white matter lesion, *TCC* thin corpus callosum, *PNP* polyneuropathy. Adapted from [39, 50]

should be treated according to established guidelines. If parkinsonism is a feature of the clinical phenotype, L-DOPA or dopamine-receptor agonists may be a treatment option. If dystonia is a prominent presentation of the HSP, botulinum toxin or even deep brain stimulation may be beneficial. In patients with SPG1 who develop hydrocephalus, shunt implantation is required [39, 40]. Regular clinical reevaluations of patients once or twice yearly are recommended to identify complications and progression of the disease.

8.5 Rare Cases

8.5.1 Cervical Flexion Myelopathy

A number of cases of spinal cord disease due to protracted fixed cervical spine positions – predominantly in young individuals – have been reported in the course of surgeries requiring a flexed cervical spine position, unconsciousness due to medication overdose, or after an assault forcing the victim into a flexed cervical spine position for a prolonged period of time [55].

Pathophysiology
In the literature, the term cervical flexion myelopathy is reserved for a chronic disease condition also known as Hirayama syndrome [56]. In case of Hirayama syndrome, the hypermobile dura compresses the cord microcirculation repeatedly for a short duration. As a consequence only highly susceptible neural cells within the spinal cord namely motoneurons, in the ventral horn are affected with isolated lower motoneuron signs and minimal MRI changes. In contrast, in case of subacute cervical flexion myelopathy, the shift of the dura over longer periods of time (hours to days) may compromise larger-caliber blood vessels (posterior spinal artery, epidural veins), causing more extensive circulatory problems affecting the white matter structures predominantly in the dorsal half of the spinal cord.

Clinical Presentation
After a protracted period of fixed cervical spine position, patients present with tetraparesis/tetraplegia meaning bilateral sensorimotor dysfunction in the upper and lower extremities including bladder and bowel dysfunction.

Diagnostics
If a subacute flexion myelopathy is suspected, spinal MRI should be performed to exclude compressive causes of spinal cord disease, in particular intraspinal hemorrhage. Within the cord parenchyma MRI longitudinally extending, dorsally accentuated signal changes with signs of cord swelling can be observed in T2-weighted sequences.

Therapy
Effective treatment options are not available. The existence of such a pathomechanisms potentially leading to irreversible neurological dysfunction should raise the awareness to check the necessity for surgeries requiring intra- or postoperative flexed cervical spine positions very carefully, particularly in young individuals, who are predominantly affected by subacute cervical flexion myelopathy. In cases where respective positions cannot be avoided, intra-/postoperative neuromonitoring should be considered to detect spinal cord dysfunction before irreversible damage to neural tissue occurs [55].

8.5.2 Epidural Lipomatosis

The spinal epidural lipomatosis is a rare entity. A majority of male patients and a mean manifestation at the age of 43 are described in the literature. Most of the cases are associated with obesity, chronic use of steroids, Cushing's syndrome, and other endocrinopathies. Only a small group of patients without relevant concomitant diseases (idiopathic spinal epidural lipomatosis) are described so far. In all these cases, manifestation of the lipomatosis was restricted to the thoracic and lumbar segments of the spinal cord especially in the dorsal and lateral parts of the myelin [57].

Pathophysiology
Excess adipose tissue deposits in the spinal canal cause radiculopathy or spinal cord compression.

Clinical Presentation
Main symptoms are back pain, followed by a slowly progressive weakness of the legs, sensory loss, and sometimes a radicular manifestation or a claudication mainly seen with a lumbar affection of the spinal cord. An autonomic dysfunction with bowel and urinary incontinence is not typical.

Diagnostics
MRI shows a peculiar signal intensity in the T1-weighted sequences. Myelography is helpful to detect an obstruction in the CSF circulation. Often associated with the spinal epidural lipomatosis are degenerative processes of the spine [58]. CSF analysis typically reveals high protein levels with mild pleocytosis reflecting compromised CSF circulation.

Therapy
Due to the small amount of cases, no evidence-based therapeutic strategies are available. In general a conservative therapy is proposed with minor symptoms, e.g., weight reduction and reduction of steroid intake. On the other hand, a surgical intervention to reduce epidural fat should be preferred with major functional deficits. The success rate meaning complete functional recovery varies between 20 and 60 % dependent on localization and etiology.

In conclusion, spinal epidural lipomatosis should be regarded as a possible differential diagnosis when a patient presents with the typically slowly progressive para-/tetraparesis and sensory deficits especially if predisposing factors are present (see chapter 7). Without specific signal enhancements indicating a spinal cord injury in the MRI, the relevant compression caused by epidural fat can be elucidated by myelography in combination with a below-block CSF analysis.

8.5.3 Conversion (dissociative) Paraplegia

The term dissociative paraplegia refers to an alteration or loss of function in the lower limbs without an anatomical or physiological explanation. This type of illness belongs to the group of conversion disorders. The average prevalence of conversion disorders in the general population is estimated at 5–22 cases per 100,000 persons. In the absence of mental state abnormalities, dissociative paraplegia remains a diagnostic and therapeutic challenge on the borderline between neurology and psychiatry [59].

Clinical Presentation
The disease condition is commonly observed in young female patients. Neurological examination yields findings, which are not congruent with a lesion of the central or peripheral nervous system. Respective patients typically present with complete paralysis of the lower extremities. In case of an "incomplete" paraparesis, flexor and extensor muscles are equally affected contradicting an expected central paresis pattern, where flexor muscles are more severely affected than extensor muscles. While examining the patient in a supine position, lifting the legs off the bench is not possible. However, walking on tiptoe or heels is possible. The Hoover sign represents another test to unmask a nonorganic origin of the presented symptoms: direct testing of the hip extension reveals weakness in the respective muscle. While testing contralateral hip flexion against resistance, ipsilateral hip extension becomes suddenly strong. Patients, who are still able to walk frequently, display a dragging gait with external or internal hip rotation. Tendon reflexes are usually unremarkable. Structured clinical interviews usually do not identify any acute or chronic psychiatric comorbidity.

Diagnostics
Appropriate diagnostic tests have to be performed to rule out a somatic cause for the disease. Therefore, imaging studies – ideally MRI of the complete neuraxis (spine and brain) – have to rule out spinal cord compression or a non-compressive lesion of the spinal cord, cauda equina, or relevant areas in the brain (e.g., parasagittal cortical syndrome due to anterior cerebral artery infarction or meningioma located in the falx). Once respective studies do not show pathological changes, inflammatory/infectious causes are addressed with CSF analysis. The integrity of descending motor and ascending sensory pathways can be objectively assessed with MEP and SSEP workup.

Therapy
To prevent disease chronification, it is suggested that patients should be informed early about the diagnosis and treated subsequently. Therefore, it is necessary to conduct a multifunctional approach therapy, including psychotherapy, relaxation techniques, autogenic training, and intensive physical therapy. Physical therapy especially might help the patient to give up symptoms without losing face and consequently improve bodily experience, movement ability, interpersonal attunement, and social well-being. There is also some evidence suggesting that patient education regarding the underlying mechanisms is helpful, but special attention must be paid

to possible stigmatization and labeling of the patient. Emphasis should be placed on the reversibility and good prognosis of the disorder [60]. A major challenge can be to protect patients with dissociative paraplegia in the long run from potentially harmful surgical interventions.

Conclusion

This chapter provided an overview about rare spinal cord disease entities, which are in many instances challenging to diagnose. Careful compilation of the past medical history including family history and clinical neurological examination represent key instruments leading to the correct diagnosis. Specific ancillary tests (e.g., specific blood chemistry analysis, genetic testing) besides imaging studies and CSF analysis are needed to confirm the suspected diagnosis, in particular metabolic causes (copper/cobalamin deficiency).

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Syringomyelia

9

Jörg Klekamp

Abstract

Syringomyelia is not a disease in its own right but a manifestation of another disease process, which incorporates either an obstruction of cerebrospinal fluid (CSF) flow in the spinal canal, tethering of the spinal cord, or an intramedullary tumor. Whenever a syrinx is demonstrated, clinical examination, analysis of the patient's history, and neuroradiological imaging have to identify the underlying cause of the syrinx. If this cause can be identified and treated successfully, the syrinx will regress, and clinical symptoms will improve or remain stable in the future.

The significance of spinal arachnopathies for development and treatment of syringomyelia in patients without a craniospinal malformation, a spinal dysraphic malformation, or an intramedullary tumor is still not widely recognized. This chapter describes diagnostic and management algorithms for spinal arachnopathies leading to syringomyelia with a special emphasis on posttraumatic syringomyelia as well as long-term results for these patients.

9.1 Introduction

The term syringomyelia was introduced by Ollivier d'Angers in 1827 [35] for cystic cavitations of the spinal cord. Syringomyelia describes a progressive accumulation of fluid inside the spinal cord. Up to this day, no pathophysiological concept for the development of syringomyelia is generally accepted. However, with the introduction of modern imaging techniques in the 1970s and 1980s, it became clear that a syrinx is always associated with additional pathologies in the spinal canal or

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craniocervical junction. This observation has changed treatment concepts for these patients in a fundamental way. If the associated pathology can be treated successfully, no further measures for the syrinx are needed. It is now widely accepted that syringomyelia is related to intramedullary tumors or pathologies that cause a disturbance of cerebrospinal fluid (CSF) flow or spinal cord tethering, i.e., fixation of the cord to the spinal dura by a thick filum terminale or other dysraphic lesions [17]. Table 9.1 gives an overview on the different pathologies related to syringomyelia in the author's series. About 74.5 % of patients with a Chiari I malformation developed a syrinx. Except for foramen magnum arachnoiditis, no other pathology causes syringomyelia in such a high proportion (Table 9.1).

Currently, syringomyelia is considered as an accumulation of extracellular fluid of the spinal cord [11, 17]. In case of intramedullary tumors, it is generally believed that alterations of the blood-spinal cord barrier play a major role [31]. But this may not be the only mechanism. It is noteworthy that infiltrating intramedullary tumors rarely produce syringomyelia, whereas a syrinx is a common feature of displacing neoplasms [24]. More information is available on the effects of CSF flow obstructions on the spinal cord from animal [27] as well as computer models [3]. Pressure changes in the subarachnoid space related to CSF flow obstructions may alter the distribution of extracellular fluid inside the spinal cord [27] which may then lead to syringomyelia [11, 17, 26]. Increased flow in the perivascular spaces has been implicated for this effect [2, 4, 17, 27, 43, 44]. If flow capacities in the extracellular space are exceeded, there appears to be an evolution from spinal cord edema, i.e., the so-called presyrinx state, to syringomyelia [8]. Intramedullary neoplasms and cord tethering may alter extracellular fluid movements to similar effects. Once syringomyelia has developed, the increased intramedullary pressure [32] and fluid movements inside the syrinx [1, 46] may lead to spinal cord damage [10, 39, 42] and progressive neurological symptoms.

Table 9.1 Pathologies associated with syringomyelia

Diagnosis	Total	Syringomyelia
Craniocervical junction	*756*	*556*
Chiari I	651	485 (74.5 %)
Chiari II	45	29 (64.4 %)
Foramen magnum arachnoiditis	33	33 (100 %)
Posterior fossa tumors	12	2 (16.7 %)
Posterior fossa arachnoid cysts	11	5 (45.5 %)
Spinal canal	*2143*	*853*
Posttraumatic arachnopathies	150	150
Nontraumatic arachnopathies	333	333
Intramedullary tumors	345	143 (41.4 %)
Extramedullary tumors	608	88 (14.5 %)
Extradural tumors	469	12 (2.6 %)
Tethered cord syndromes	170	59 (3.5 %)
Degenerative disc disease	68	68

9.2 Diagnosis

Intramedullary tumors associated with syringomyelia always display contrast enhancement on MRI. The most common entities are ependymomas (Fig. 9.1) and angioblastomas (Fig. 9.2). Whereas ependymomas associated with syringomyelia are solid space-occupying tumors, which are easily detected on MRI after application of gadolinium (Fig. 9.1), the diagnosis of an angioblastoma may not be straightforward. They tend to be localized in the dorsal root entry zone of the cord and may be quite small [24] (Fig. 9.2).

If tethered cord syndromes cause syringomyelia, these syrinx cavities tend to be rather small and of no clinical significance (Fig. 9.3). A large syrinx of the entire cord is rarely observed in patients with a tethered cord syndrome. The diagnostic challenge in these patients is the identification of all tethering elements, which tend to be localized below the lower pole of the syrinx. Such elements, which can be found in various combinations in a particular patient, are a thickened filum terminale, a split cord malformation (Fig. 9.3), or a lipoma fixed at the dura to mention the most frequent [19].

In patients with Chiari malformations, CSF flow can be compromised by cerebellar tonsils filling the space of the cisterna magna, by arachnoid scarring in the foramen magnum area, and by obstruction of the foramen of Magendie (Fig. 9.4). Whereas the obstruction by cerebellar tonsils is clearly apparent on a preoperative

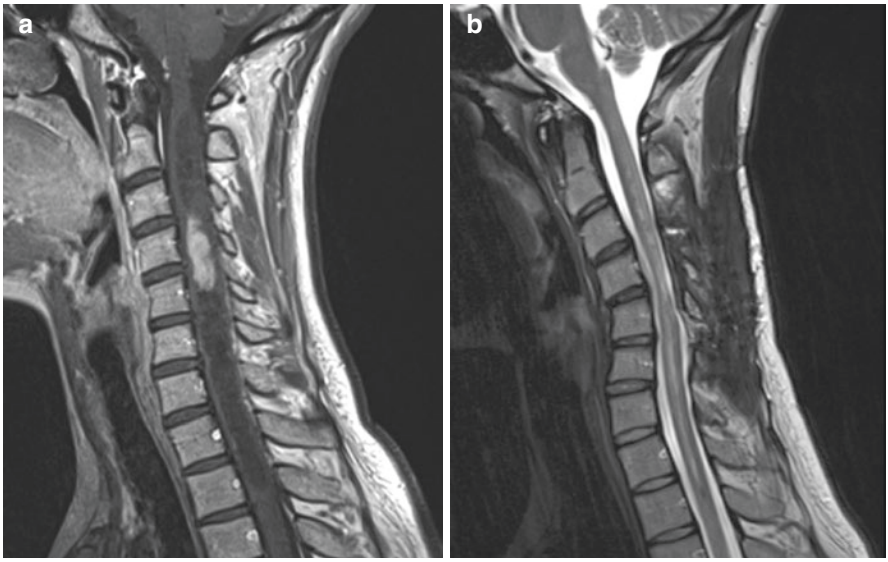

Fig. 9.1 (**a**) This T1-weighted MRI with gadolinium demonstrates an ependymoma at C4–C5 with associated syringomyelia above and below the tumor in a 26-year-old woman. The tumor shows bright contrast enhancement and is well demarcated from the surrounding cord tissue. (**b**) The postoperative scan shows the complete collapse of the syrinx after tumor removal. Despite reinsertion of the laminae, a kyphotic deformity developed

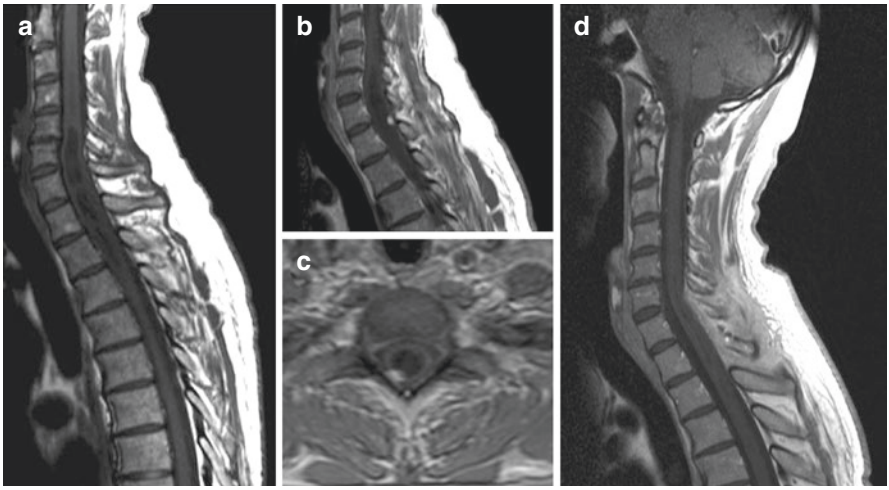

Fig. 9.2 (**a**) This T1-weighted MRI image of a 56-year-old man shows a syrinx between C5 and Th3. (**b**) After gadolinium application a small angioblastoma appears posteriorly at C7/Th1. The corresponding axial scan demonstrates the typical location of this tumor in the posterior root entry zone on the right side (**c**). (**d**) With removal of this tumor, the syrinx collapsed

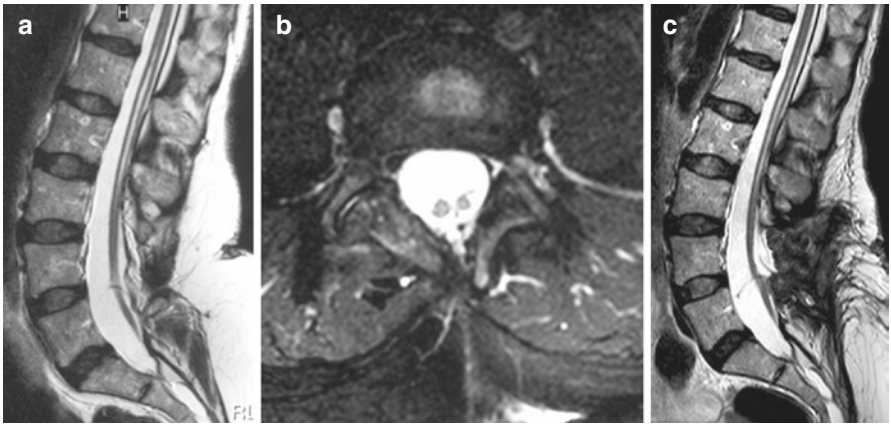

Fig. 9.3 (**a**) This T2-weighted image of a 53-year-old woman demonstrates the conus position at S1 and a small syrinx in the lower part of the cord, which exerts no space-occupying effect. (**b**) The axial scan at L4/5 shows a split cord malformation type 2 with a fibrous band splitting and fixing the cord at this level. Extradurally, this band was connected to a dermal sinus. Surgery required section of the filum terminale below S1 and untethering at L4/5. (**c**) The postoperative T2-weighted image shows no significant change of the syrinx despite complete untethering of the cord

MRI, arachnoid adhesions and an obstruction of the foramen of Magendie are mostly intraoperative findings and need special attention during surgery [18].

In posttraumatic syringomyelia, CSF flow obstruction may be caused by arachnoid scarring at the trauma level as well as narrowing of the spinal canal due to

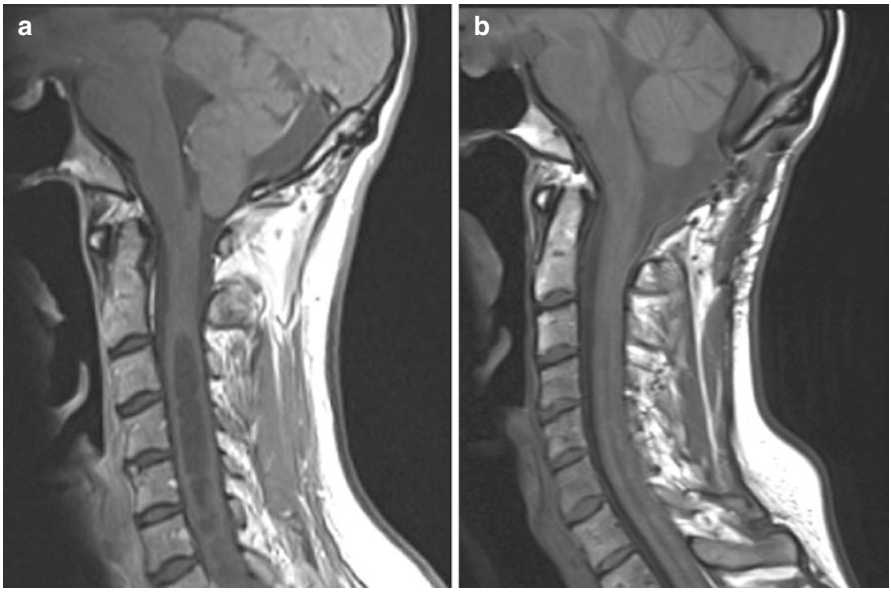

Fig. 9.4 (**a**) The T1-weighted MRI scan of a 47-year-old woman with a Chiari I malformation and a syrinx C3–Th2. (**b**) After decompression of the foramen magnum with a duraplasty, the CSF passage is free, and the syrinx has decreased

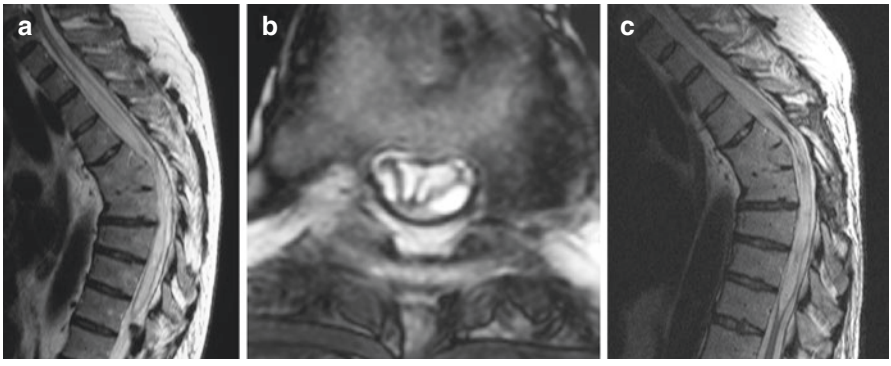

Fig. 9.5 (**a**) This T2-weighted MRI scan of a 49-year-old man shows a posttraumatic syrinx Th1–Th10 10 years after suffering a fracture at Th10 without any neurological deficits. A kyphotic deformity developed. (**b**) The axial scan at Th6 shows a posterior adhesion of the spinal cord to the dura resembling a posttraumatic arachnopathy. (**c**) The postoperative scan after arachnolysis and duraplasty at Th6 demonstrates a decrease of the syrinx (see also Fig. 9.8)

posttraumatic stenosis or kyphosis (Fig. 9.5). Furthermore, posttraumatic cord tethering may contribute to syrinx development. Depending on associated injuries to vertebral bodies and joints, MRI may not be sufficient for surgical planning. CT scans in bone window technique may be very helpful to localize and determine bony

landmarks for intraoperative orientation as well as the position of implants in patients who require a spondylodesis [21].

In the absence of a craniocervical malformation, an intramedullary tumor, or a history of spinal trauma, syringomyelia is still considered idiopathic by many physicians. However, these patients have to be evaluated very carefully for radiological and clinical signs of arachnoid pathologies in the spinal canal causing CSF flow obstructions [22] (Fig. 9.6). The syrinx starts at the level of obstruction and expands from there. If the syrinx expands in rostral direction, the obstruction will be found at the caudal end of the syrinx and vice versa. This also implies that the obstruction will most likely be found close to the largest diameter of the syrinx [22] (Fig. 9.6).

Due to the pulsatile movements of arachnoid septations, webs, or cysts, standard MRIs may not always be able to demonstrate an arachnopathy directly. With a

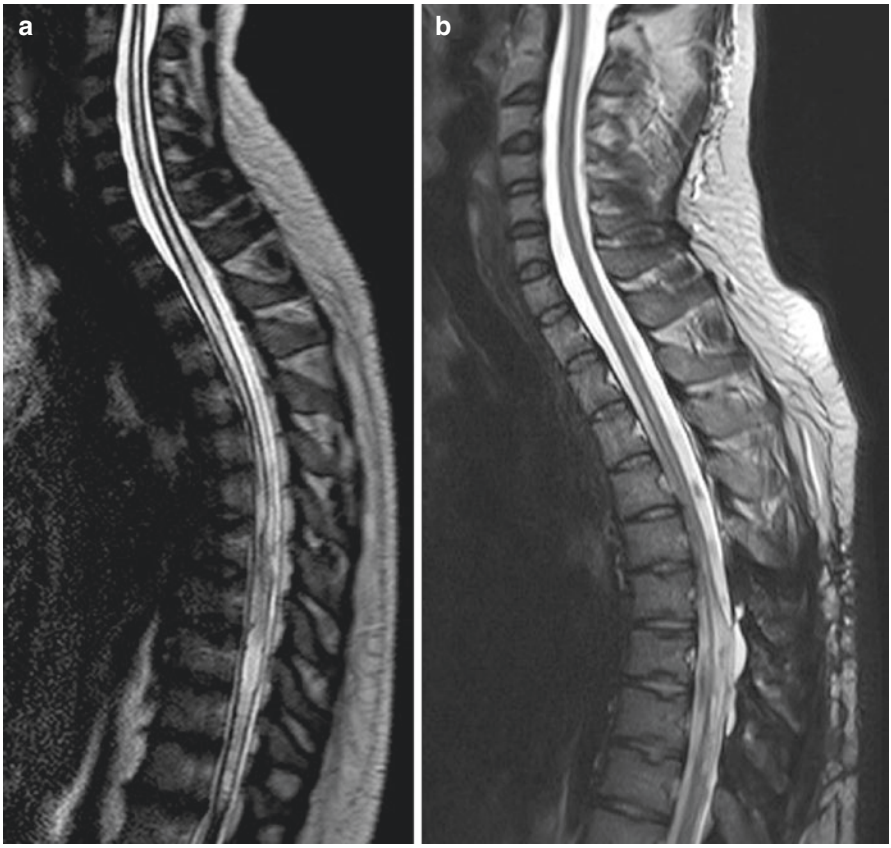

Fig. 9.6 (**a**) T2-weighted MRI scan of a 29-year-old man with a syrinx C2–Th11 and no history of trauma. At Th7 the cord appears compressed posteriorly and the syrinx caliber changes abruptly. At surgery, a circumscribed arachnopathy was evident at this level obstructing CSF flow and compressing the cord. (**b**) After arachnolysis and duraplasty at Th7, CSF flow at this level was established and the syrinx decreased

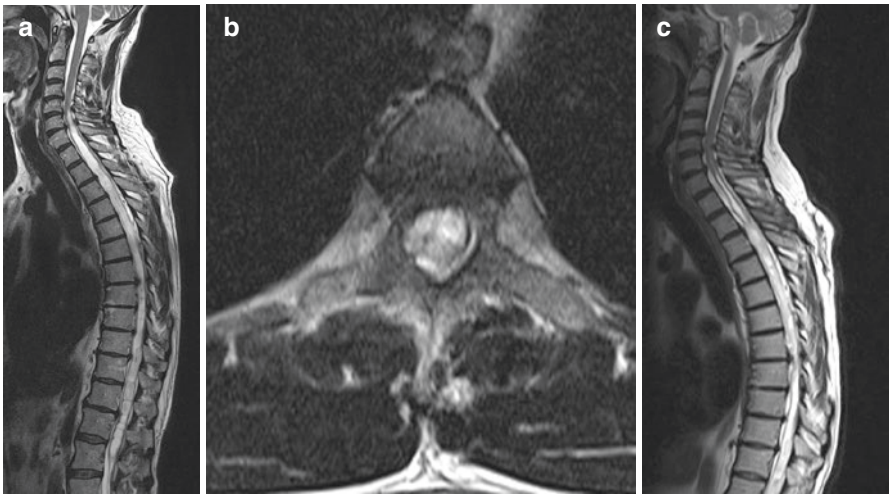

Fig. 9.7 (**a**) T2-weighted MRI scan of a 66-year-old man 5 years after suffering from a listeria meningitis. After recovery from this inflammation, the patient experienced a progressive paraparesis and ascending neurological deficits threatening his hand functions. The syrinx had reached up to C6. (**b**) The meningitis had led to severe arachnoid scarring around the entire cord from Th3 to Th10 as shown on the axial scan. (**c**) After placement of a thecoperitoneal shunt at the cervicothoracic junction lowering the subarachnoid pressure above the arachnopathy, the cervical and upper thoracic part of the syrinx has decreased as shown on this MRI after 6 months

history of spinal meningitis or subarachnoid hemorrhage [5], the often quite extensive arachnopathy is rather easy to diagnose by MRI (Fig. 9.7). Many arachnopathies, however, are quite discrete and extend over a few millimeters only (Fig. 9.6). Cardiac-gated cine MRI should be employed for such instances to study spinal CSF flow to identify areas of flow obstruction which may correspond to such circumscribed arachnoid pathologies [1, 22]. Sometimes significant flow signals can also be detected in the syrinx itself. In such cases, the highest flow velocities in the syrinx can be expected adjacent to the arachnoid scarring. The spinal cord should be studied with thin axial slices in T2-weighted images over the entire extent of the syrinx to search for areas of cord compression, displacement, or adhesion to the dura [7, 14, 22]. In the sagittal plane, the contour of the cord may appear distorted in areas of arachnoid scarring (Fig. 9.6). CISS (constructive interference in steady state) sequences can be used not only for the demonstration of the syrinx [12] but may also be helpful to detect arachnoid webs, scars, and cysts, because this technique is less susceptible to CSF flow artifacts [12]. Myelography and postmyelographic computer tomography (CT) are alternative methods to demonstrate arachnoid pathologies but have a lower sensitivity [22].

The sequence of events leading to a syrinx has implications not only for the neuroradiological appearance as just described but also for the evolution of clinical symptoms. The syrinx develops as a consequence of a series of events that originate from a pathology leading to CSF flow obstruction. For almost all entities leading to syrinx development, this process requires many years. Therefore, the first neurological

symptoms in the patient's history are commonly caused by this underlying pathology rather than the syrinx. In other words, a carefully taken clinical history can provide clues to the underlying pathology. If neurological signs spread to other parts of the body in an ascending pattern, the cause of the syrinx will be located at the lower pole of the syrinx and vice versa similar to the radiological evolution of the syrinx. Apart from trauma, arachnoid scarring may be related to infection [16] (Fig. 9.7), hemorrhage [5], irritation by outdated contrast agents such as pantopaque [28], or surgery, to mention a few [22].

It is always puzzling that patients may harbor a huge syrinx and yet have just minor symptoms with exactly the opposite observation for some smaller syrinx cavities associated with major neurological deficits. One explanation for this paradox may be that a great deal of the clinical problems are related to the underlying disease process causing the syrinx rather than to the syrinx itself [25]. This is particularly evident for syringomyelia associated with intramedullary tumors or cord tethering.

The classical symptom of syringomyelia is a dissociated sensory loss with loss of sensation for temperature and pain but preserved sensation for light touch. Pain related to syringomyelia is either permanent or aggravated by maneuvers such as coughing and sneezing and perceived in dermatomes corresponding to the level and extension of the syrinx. Syrinx pain represents neuropathic pain. In order to produce neuropathic pain, a syrinx must have reached the region of the dorsal horns close to the dorsal root entry zone. Quite commonly, patients report that their pain was associated with coughing or sneezing initially before becoming permanent. Other types of pain which patients report quite often, such as pain associated with exertion, cannot be explained by syringomyelia and are caused by other mechanisms such as muscular spanning to mention a common example. Late symptoms of syringomyelia are muscle atrophies corresponding to damage of ventral horn cells or trophic changes leading to skin and joint damages, particularly in the shoulder and elbow [25].

9.3 Management

Successful treatment of syringomyelia requires to treat the underlying cause – preferably before significant neurological deficits have developed. For syringomyelia associated with intramedullary tumors and Chiari I malformation, the rates for postoperative syrinx resolution are above 80 %, provided the tumor is removed and all components contributing to CSF flow obstruction in Chiari malformations have been surgically addressed, respectively [18, 20]. Syrinx cavities related to tethered cord syndromes tend to be of small caliber and extension. Therefore, complete untethering caused a postoperative reduction in just 13 %, whereas the syrinx remained unchanged in 87 % [19].

Successful treatment of syringomyelia related to spinal rather than craniocervical CSF flow obstructions is much more challenging. The underlying causes are more difficult to identify and to deal with surgically. For this reason, surgery on spinal arachnopathies for treatment of syringomyelia should be reserved for patients with progressive symptoms. Nevertheless, treating the cause of the syrinx with arachnolysis, untethering the cord, and duraplasty is rewarded by considerably better results compared to syrinx shunting procedures [21–23, 25, 33, 37].

Neuropathic pain and dysesthesias, particularly those of burning character, may be major clinical problems. Even though these may improve to some degree with successful treatment of the syrinx, this is never certain. Therefore, the decision for or against surgery should be based on the course of neurological signs and symptoms rather than pain syndromes alone [22].

In general, surgery can be recommended for patients with arachnoid scarring limited to about 2–3 spinal segments [22] (Fig. 9.5). All operations are performed in prone position. Laminotomies are recommended to reinsert the lamina at the end of the operation with titanium miniplates. After exposure of the dura, the extent of the arachnoid pathology and the syrinx can be visualized with ultrasound. Pulsations of syrinx fluid and CSF may become visible. Most importantly, the safest spot for opening of the dura can be chosen with this technique. As contamination of the CSF with blood may cause inflammatory reactions of the arachnoid, great care must be taken to achieve good hemostasis. For this purpose, the entire surgical field is covered by moist cottonoids, which keep soft tissues moist and soak up any minor bleeding. Then the dura is opened under the operating microscope in the midline without opening of the arachnoid. Once the dura is held open with sutures, the arachnoid pathology can be studied, and adequate exposure cranially and caudally is ensured in order to gain access to a normal and unaffected subarachnoid space on either end (Fig. 9.8a). Obviously, any surgeon should be familiar with the normal anatomy of the spinal subarachnoid space [34]. The posterior subarachnoid space is divided in two halves by a posterior longitudinal arachnoid septum. This septum extends between the outer arachnoid layer and an intermediate layer on the cord surface. The insertion on the cord surface is related to the midline dorsal vein. Further strands of arachnoid may be encountered in the posterior and lateral subarachnoid space. These arachnoid webs and septations are a physiological feature of the thoracic spinal canal. In the cervical area, the posterior longitudinal septum may be absent, and lateral arachnoid webs between nerve roots, which are considered to promote CSF flow in the thoracic spine, are not present. Under normal conditions, no arachnoid webs or septations exist in the entire anterior spinal subarachnoid space. A good landmark for dissection are the dentate ligaments, which originate from the spinal cord pia mater, run between posterior and anterior nerve roots, and insert close to the dural nerve root sleeve. With a microdissector, arachnoid and dura can be separated from each other without any problem in areas without arachnoid scarring, i.e., at either end of the exposure. In the area of scarring, sharp dissection with microscissors is usually required to achieve this (Figs. 9.8b, c). At the level of CSF flow obstruction, the arachnoid may become densely adherent to the cord surface. With opening of the rostral and caudal subarachnoid space, CSF flushes into the surgical field, and often the cord, which was distended by the syrinx, starts to pulsate, and the syrinx may collapse at this point. The arachnoid scar can be resected layer by layer leaving a last sheath on the cord surface to avoid injury to the cord or surface vessels (Figs. 9.8d, e). This last layer resembles the intermediate arachnoidal layer mentioned above. In this way, a free CSF passage in the posterior subarachnoid space can be created in every patient across the region of the arachnopathy. Dissection is then continued laterally on either side toward the dentate ligaments. This leads to a complete untethering of the cord in the majority of cases. No arachnoid dissection should be performed anteriorly of the dentate

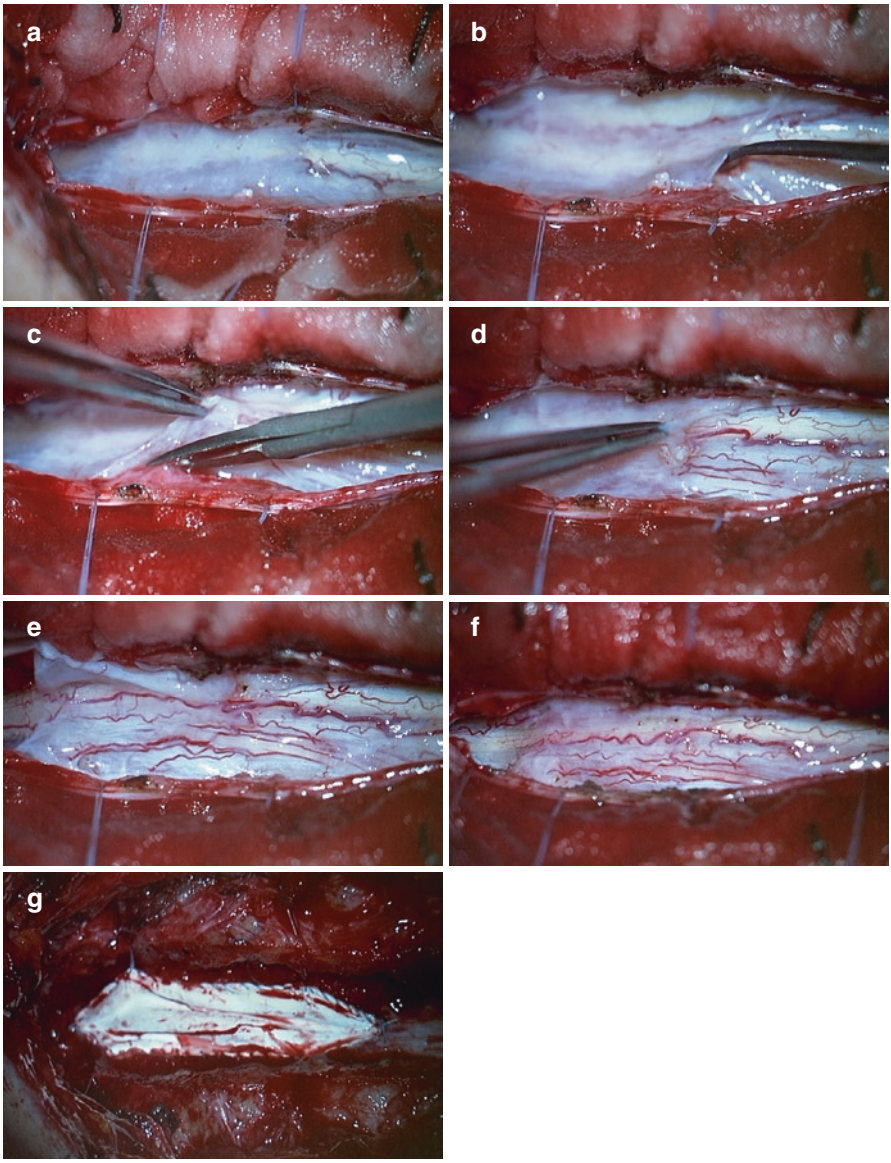

Fig. 9.8 (**a**) This intraoperative view after dura opening shows the posttraumatic arachnopathy at Th6 corresponding to Fig. 9.5. The arachnoid appears translucent in the right half of the exposure marking the lower end of the pathology. (**b**) The arachnoid is adherent to the dura requiring sharp dissection to separate it (**c**). Starting below the arachnopathy, the arachnoid is incised and dissected off the spinal cord. The arachnopathy is gently held under slight tension with microforceps (**d**) and cut preserving the blood vessels on the cord surface which are embedded in it (**e**). (**f**) At the end of the intradural dissection, a free CSF passage is established across the arachnopathy. Note the thin arachnoid layer left on the spinal cord covering its vessels. (**g**) A duraplasty has been inserted and lifted up with tenting sutures to enlarge the subarachnoid space limiting reobstruction by postoperative scar formation

ligaments to avoid injuries to motor pathways and anterior spinal cord vessels. Closing the microsurgical part of the operation, an expansile duraplasty is inserted with a tight running suture and finally lifted up with tenting sutures on either side (Fig. 9.8f). To avoid scar formation and tethering between duraplasty and the spinal cord, alloplastic material for duraplasty should be preferred, i.e., Gore-Tex® (W.L. Gore & Associates GmbH, 85640 Putzbrunn, Germany). Special attention is finally paid to a good, tight closure of the muscle layer to prevent any CSF from entering the epifascial space. In patients who have been operated before, as in patients with posttraumatic syringomyelia who underwent spinal instrumentation, for instance, a lumbar drain is placed prophylactically if the soft tissue appears scarred and sparsely vascularized.

Considerable experience is needed to be successful with this surgical technique. The more focused the surgery, the less scarring may result. If unnecessary steps are taken, such as a too extensive dura opening, or the surgical field is contaminated with considerable amounts of blood, postoperative scarring may counterbalance completely the effect of surgery. On the other hand, if the dura opening is not extensive enough to gain access to the normal subarachnoid space above and below the level of scarring, the procedure is insufficient. As always, it is the right measure that counts and determines whether an operation will be successful or not.

For patients with more extensive arachnopathies after meningitis (Fig. 9.7), multiple intradural surgeries, or spinal subarachnoid hemorrhage, for example, surgery cannot provide a normal CSF passage anymore [22, 25]. Axial MRIs taken from the entire area of the arachnopathy should be evaluated in such instances for evidence of cord compression. Quite often, pouches and cysts have formed causing profound cord compression over a few spinal segments. Such compressions can be treated surgically by a wide fenestration of the corresponding arachnoid membranes. Such an operation can improve neurological symptoms related to the cord compression, but it will not influence the syrinx.

For that purpose, thecoperitoneal shunts have been introduced, which drain CSF from the subarachnoid space above the level of obstruction to the peritoneal cavity [29, 36, 45, 47, 48] (Fig. 9.7). For cavities extending into the cervical cord, ventriculoperitoneal shunts have been used for the same purpose [38, 50]. However, these shunts have their problems. There is little experience concerning the correct pressure settings other than to set them as low as possible avoiding signs of overdrainage or low intracranial pressure. Programmable shunts are sometimes used, but the shunt systems available are not specifically designed for this purpose. No data exist, as to how much tissue coverage may be allowed over the valve in order to still be able to change the setting with the programming device. This leaves the problem where to position the valve. Low-pressure valves have been used to overcome these problems. Five patients in the author's series were treated that way. In one patient, a low-pressure valve was still not low enough, so that the valve was removed leaving the patient with a valveless drain. This worked for a year after which the catheter got blocked. Two patients do well clinically with a low-pressure valve even though the syrinx did not regress. The remaining two patients demonstrate a profound decrease of the syrinx with a favorable clinical response (Fig. 9.7).

For patients with a complete cord lesion, cordectomy is a very effective form of treatment for syringomyelia [6, 9, 15, 30, 41, 49] (Fig. 9.9). All patients treated in

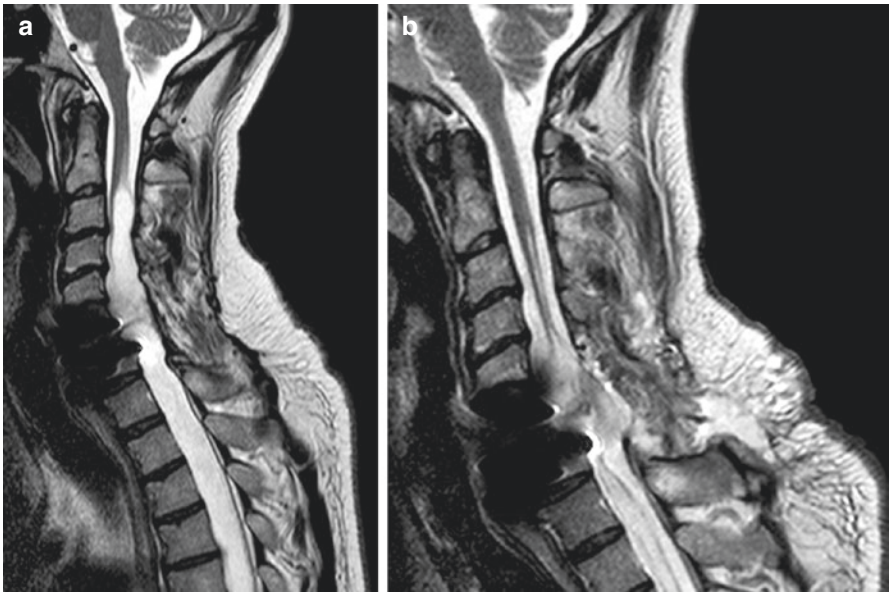

Fig. 9.9 (**a**) This T2-weighted MRI scan shows a huge posttraumatic syrinx almost 20 years after a complete cord lesion due to a dislocated C7 fracture in a 46-year-old man with progressive motor weakness of his hands. A first surgical attempt with arachnolysis and duraplasty at C6/7 stabilized the neurological status for 30 months. (**b**) The postoperative scan after cordectomy at C7 demonstrates the complete collapse of the syrinx

this manner in the author's series improved neurologically with permanent resolution of the syrinx. However, the psychological burden for a patient to accept this operation should not be underestimated. Most patients prefer to undergo a decompression first. After all, this operation does provide good results in the majority of patients [9]. Patients will accept a cordectomy, however, if the ascending neurology cannot be arrested by decompression or shunting procedures and the neurological progress threatens important functions such as respiratory or hand muscles.

9.4 Results

Concentrating on patients with syringomyelia related to spinal arachnopathies, 150 patients with posttraumatic arachnoid scarring and 333 patients with nontraumatic arachnopathies were encountered in the author's series. Reserving surgery for patients with progressive neurological symptoms led to operations for 73 patients with posttraumatic and 103 patients with nontraumatic arachnopathies (Table 9.2). Overall, 190 decompressions aiming at improving CSF flow and decompressing the spinal cord by resecting arachnoid pathologies were performed, while 11 patients with complete paraplegia underwent cordectomies, and 5 thecoperitoneal shunts were implanted. One patient received an opiate pump for

Table 9.2 Operations for spinal arachnopathies

Type of surgery	Posttraumatic arachnopathies	Nontraumatic arachnopathies	All
Decompression	69	121	190
Cordectomy	10	1	11
Thecoperitoneal shunt	1	4	5
Ventral fusion	5	4	9
Posterior fusion	7	4	11
Opiate pump	1	–	1

Table 9.3 Neurological recurrence rates for spinal arachnopathies

Patient group	5 years (%)	10 years (%)	*P*
All	34.2	52.4	
Nontraumatic focal	20.4	31.1	<0.0001
Nontraumatic extensive	67.3	72.8	
Nontraumatic all	35.2	44.9	
Posttraumatic no cord injury	22.0	22.0	n.s.
Posttraumatic incomplete cord injury	39.9	73.7	
Posttraumatic complete cord injury	32.0	54.6	
Posttraumatic all	31.8	60.9	

his neuropathic pain syndrome. The remaining operations dealt with degenerative diseases of the cervical spine.

Concentrating on the 190 decompressions with arachnolysis and duraplasty, complications were observed in 18.5 %. The most common were wound infections in 4.2 % and postoperative urinary tract infections in 4.8 %. CSF fistulas were observed in just 1.8 %. Permanent surgical morbidity defined as permanent neurological worsening within 1 month after surgery occurred after seven operations, i.e., 3.7 %. A postoperative decrease of the syrinx was observed in 68.5 %, 25.9 % showed no postoperative change, while 5.6 % increased further despite surgery. After 3 months, 51.5 % considered their condition improved, 40.1 % as unchanged, and 8.4 % as worsened. Looking at individual symptoms revealed postoperative improvements for sensory deficits and pain, whereas motor weakness, gait, and sphincter functions were left unchanged.

Long-term results were determined with Kaplan-Meier statistics to determine the rates for progression-free survival after decompression. Overall, 65.8 % remained in a stable neurological status for 5 years after surgery. This rate was reduced to 47.6 % after 10 years. Looking at particular subgroups revealed good long-term results for patients with a focal nontraumatic arachnoid pathology not exceeding two spinal segments (Fig. 9.6) and for posttraumatic patients who had conceded no spinal cord injury at the time of the accident (Table 9.3) (Fig. 9.7). For these subgroups, significantly lower clinical recurrence rates were determined after 10 years.

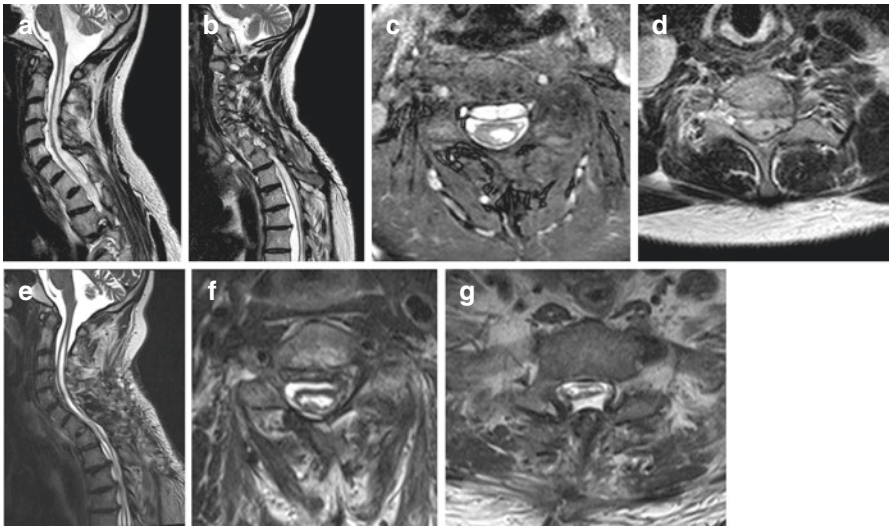

Fig. 9.10 (**a**) This T2-weighted MRI scan of a 53-year-old man shows a posttraumatic syrinx C2–Th5 related to a spinal injury at C7/Th1, which had resulted in an incomplete spinal cord injury 18 years earlier. The syrinx was caused by arachnoid scarring at the injury level combined with a narrowing of the subarachnoid space due to a posttraumatic dura dissection between inner and outer layer of the dura anteriorly from C2 down the entire thoracic spine (**b**). (**c**) This axial scan at C6 shows the syrinx in the posterior left of the cord. The dissection is caused by a rupture of the inner dural layer in the root sleeve C6/7 on the left side (**d**). At surgery, the CSF passage was established at the cervicothoracic junction, and the dura defect in the root sleeve was closed with muscle and fibrin glue. Postoperatively, the sagittal T2-weighted MRI demonstrates a reduction of the syrinx as well as the dura dissection (**e**). The axial scans at C6/7 (**f**) show fibrin glue in the left root sleeve and the dissection anteriorly as well as the duraplasty and free CSF space at Th1 (**g**)

Patients with extensive arachnoid pathologies or those with an incomplete spinal cord injury (Fig. 9.10), on the other hand, are the most difficult patients with spinal arachnopathies to treat. For patients with extensive arachnopathies after meningitis or intradural hemorrhages, the surgical concept of arachnolysis and duraplasty is as problematic as any other form of surgical treatment.

Thecoperitoneal shunts may reduce the ascending syrinx, but they hardly influence the myelopathy for which the arachnopathy itself is responsible (Fig. 9.7). The same applies to syrinx shunts. For patients with posttraumatic syringomyelia after an incomplete cord lesion, compromises as how far the arachnolysis and untethering of the cord should be pursued are unavoidable if surgical morbidity risking the remaining spinal cord functions is kept to a minimum (Fig. 9.10). It remains to be seen whether long-term results will improve with further experience. For patients with a posttraumatic syringomyelia who had suffered a complete spinal cord lesion at the time of their accident, results are more favorable, because a complete untethering and arachnolysis at the injury level can be performed without risking further neurological deficits (Fig. 9.11). If new symptoms appear postoperatively and the syrinx expands again, a cordectomy can always be performed later on (Fig. 9.9).

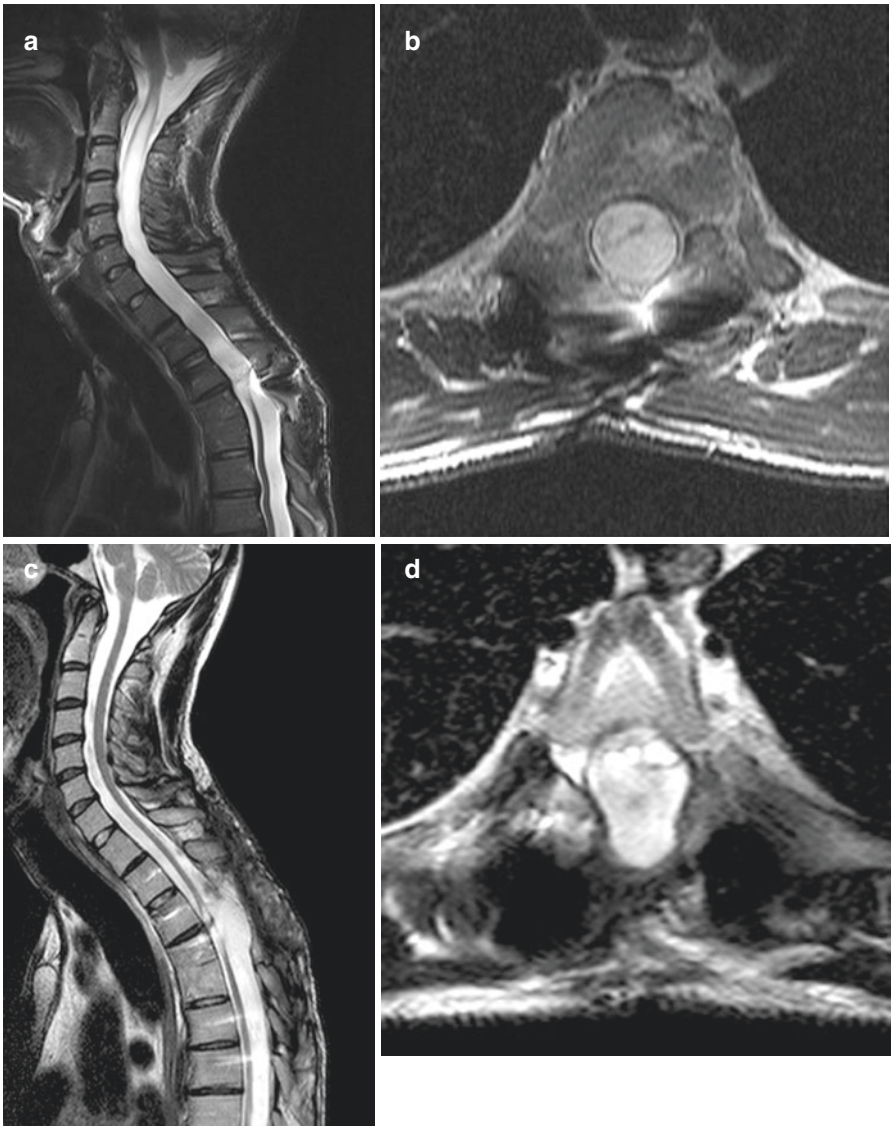

Fig. 9.11 (**a**) T2-weighted MRI scan of a 28-year-old man 6 years after an accident with fracture at Th4 and a complete spinal cord lesion. A huge syrinx has formed from C1 to Th4. (**b**) The axial scan at Th4 demonstrates the compression of the cord from posterior. After arachnolysis and duraplasty at Th4, the postoperative sagittal (**c**) and axial (**d**) scans show the complete collapse of the syrinx and the free CSF pathway at the injury level

Conclusion

The diagnosis of syringomyelia should be reserved for patients with a space-occupying intramedullary cyst of progressive character and differentiated from such entities as a dilatation of the central canal or myelomalacia [13, 25, 40]. Syringomyelia is not a disease in its own right but a manifestation of a disorder

of the spinal canal or craniocervical junction that has either resulted in an obstruction of CSF flow or spinal cord tethering or is associated with an intramedullary tumor. Management of patients with syringomyelia requires the correct diagnosis of the underlying disorder and the successful treatment of it. As this can be done in the vast majority of patients, no further surgical measures for the syrinx are required. Shunting the syrinx in particular can and should be avoided as the first line of treatment. The long-term prognosis depends on the therapeutic outcome of the underlying disorder.

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Part III

Diagnostics

Spinal Cord Imaging

10

Patrick W. Stroman and Rachael L. Bosma

Abstract

Imaging methods such as X-ray-based methods and magnetic resonance imaging (MRI) have had a substantial impact on the ability to diagnose spinal cord injury and disease. X-ray-based methods including computed tomography (CT) provide detailed information about anatomical changes in dense materials (bone, cartilage) after traumatic injury, disc degeneration, etc. MRI methods, on the other hand, provide information about soft tissue changes such as gray matter and white matter in the spinal cord, or vascular changes. Fine detail can also be obtained about changes in tissue structure at the cellular level via changes in magnetization relaxation times, magnetization transfer, and changes in water self-diffusion. Even with these capabilities, current clinical imaging methods cannot yet assess functional changes due to traumatic or nontraumatic injury or disease. Current research to develop functional magnetic resonance imaging (fMRI) in the spinal cord shows the potential for future clinical applications. However, there are technical challenges yet to be overcome, and the reliability and specificity of the methods need to be demonstrated. The process of developing fMRI and diffusion tensor imaging (DTI) methods for the spinal cord has resulted in methodological advances that contribute to improvements in all MRI methods for imaging the spinal cord. This chapter outlines the current capabilities of spinal cord imaging methods and the future potential to overcome as yet unmet needs.

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10.1 Introduction

Noninvasive imaging methods provide essential access to information about the condition of the spinal cord after an injury has occurred (both traumatic and nontraumatic). The imaging modalities available include X-ray-based methods, such as plain film X-ray and computed tomography (CT), magnetic resonance imaging (MRI) methods, and positron emission tomography (PET). In broad terms, X-ray-based methods provide anatomical information about the dense structures, such as the bone in the spine. MRI methods provide information about soft tissues in the spinal cord and the surrounding anatomy, in the form of anatomical detail, structural composition, and information about neural function. PET provides information about the metabolic demands of the tissues. For the purposes of clinical imaging, the choice of the imaging method, and the value of the information provided, therefore depends critically on the clinical stage of care. For example, in the acute stage, shortly after admission to the hospital, the most urgent information may be to determine whether or not damage to the spine and spinal cord has occurred, and X-ray and CT are widely used. However, MRI may also be of great value, depending on the type or mechanism of suspected injury. During stages of recovery, and evaluation of the effects of injury, or for planning of surgical interventions or rehabilitation strategies, MRI may be considerably more valuable because of the information it can provide about the neural tissue in the spinal cord itself. PET, on the other hand, is used for assessing the functional condition of the spinal cord. For the purposes of clinical research, and emerging technologies, the greatest advances are currently being made with MRI-based methods to show anatomical detail, structural information at the cellular level, and details about neurological function.

The purpose of this chapter is to discuss current and emerging imaging methods to provide information about traumatic and nontraumatic spinal cord injury in the clinical context, with a focus on obtaining information about neurological aspects of spinal cord injury. The chapter is therefore focused primarily on MRI-based methods. We first introduce the basic concepts underlying the various imaging methods that are widely used for imaging the spinal cord, including X-ray, CT, and MRI, and discuss their strengths and limitations. Advanced concepts underlying specialized MRI-based methods such as myelin water fraction (MWF) imaging, diffusion tensor imaging (DTI), and functional MRI (fMRI) are then introduced. We then present a case study to show how they can provide valuable information about gross anatomical, cellular structural, and neural functional changes in the spinal cord as a result of traumatic or nontraumatic injury.

10.2 X-Ray and CT Background

The earliest method of medical imaging was based on X-rays and was developed from Wilhelm Röntgen's discovery that earned him the first Nobel Prize in Physics. X-ray-based imaging methods are based on how light (electromagnetic (EM) radiation), in the X-ray range of the light spectrum, is attenuated by interactions with matter as it passes through the body. Emitters on one side of the body produce the X-rays, and

detectors record the energy that emerges from the other side. A photon of light in the X-ray range of the EM spectrum may pass through materials, such as tissues in the body, without encountering any matter, or it may interact with an electron and be absorbed or scattered. The probability of a proton being absorbed depends on the atomic number (Z) and the X-ray energy (E), being proportional to Z^3/E^3. Elements with higher atomic numbers, and more dense materials, have higher number of electrons in a given volume. A photon passing through the material therefore has a higher probability of encountering an electron, and the X-ray energy is more attenuated as it passes through the tissues. The image contrast obtained with medical X-ray-based imaging methods is therefore determined primarily by the density of materials and the X-ray energy. X-ray-based images provide high contrast between bone and surrounding tissues, and will reveal a cyst, syrinx, or tumor, because of the differences in tissue density. However these methods provide essentially no contrast between gray matter, white matter, and cerebrospinal fluid (CSF). X-ray-based imaging methods provide information about the mechanisms of why neurological function may be altered as a result of a traumatic or nontraumatic injury, but do not provide information about the changes in neurological function. For this information we turn to MRI methods.

10.3 MRI Background

Whereas X-ray-based methods rely on light transiting through the body to a detector, magnetic resonance (MR) is based on signals originating from within the body. As a result, images can be obtained without introducing any potentially harmful exposure to radiation. The signal used for MRI originates from the magnetic properties of the hydrogen nuclei (which are in fat and water and make up the majority of our body) in our body and can be produced when they are manipulated by a strong magnetic field. The following sections provide a brief explanation of the sequence of processes that are used to create an MR signal and generate an image.

10.3.1 Properties of Hydrogen

In general, elements with unpaired nuclei (protons, electrons, or neutrons) produce a net magnetic field; however we are going to focus on the hydrogen nucleus (H^1) as it is most commonly used for MR images due to its abundance in the body (~60 % of the body is made up of water). The hydrogen nucleus is a single proton which has both a magnetic field and inherent spin and angular momentum, because of this spin. Within a strong magnetic field, the proton will precess (i.e., "wobble") around the direction of the magnetic field, much like a spinning top. The rate of precession is the same for every hydrogen nucleus, but depends on the strength of the external magnetic field (B_0). This wobbling magnetic field can induce a current in a nearby electrical conductor. It is this current that we measure in MR and from it we create an image. The next sections will focus on how we get the hydrogen nuclei to precess, how we measure the current it induces, and how we know where in the body the precessing magnetic field is coming from, in order to produce an image.

10.3.2 The Body Inside a Strong Magnetic Field

In the absence of a strong magnetic field, the orientations of the axes of the hydrogen nuclei (termed the "spin directions") in the body are randomly distributed, and their individual magnetic fields cancel each other out. When a person enters a strong magnetic field, such as a 3 tesla MR scanner, the spins of the hydrogen nuclei align either parallel (low energy state) or antiparallel (high energy state) to the magnetic field (B_0). More spins will orient to the low energy state than the higher energy state and therefore impose a net magnetization in the direction of the static (B_0) magnetic field. It is important to note that when a person is placed in an MRI system, the hydrogen nuclei align with/against the direction of the magnetic field without influencing or changing any molecular structures or physiological functions, and therefore MRI is completely nonreactive.

When your body enters a strong magnetic field (B_0), the hydrogen nuclei do not instantaneously "snap" into alignment with B_0. The transition from randomly distributed spins that occurs outside a strong magnetic field environment to the arrangement that produces a net magnetization when inside a strong magnet is called "relaxation" which can take from a fraction of a second to a few seconds. It is while the hydrogen nuclei are not in alignment with B_0 that their axes precess, as described above.

Hydrogen nuclei precessing around B_0 are out of phase from one another (oriented in different directions), and therefore there can be a net magnetization in the direction parallel to B_0, called the longitudinal axis (z), but no magnetization component in the transverse (i.e., x–y) plane. This is important because the magnetic field component parallel to the longitudinal axis varies only slowly due to relaxation (or not at all at equilibrium), and we can only measure a time-varying magnetic field. Therefore, we need to push the magnetization away from the z-axis into the x–y plane, where it will precess around the z-axis and yield a time-varying magnetic field. Because of the rate of precession of the nuclei, the magnetization can be pushed away from equilibrium with another magnetic field that oscillates or rotates at the exact same frequency as the precession (the Larmor frequency). This oscillating magnetic field needs to be applied only very briefly, in a pulse, and is therefore called a radio-frequency (RF) pulse. The RF pulse acts to rotate the magnetization away from the longitudinal axis and can be calibrated to provide any amount of rotation that we want, termed the "flip angle." Note that the RF pulse rotates the spins together, from the longitudinal axis to a new orientation, and so, at least initially after the pulse, they are in phase with one another (no longer canceling out). As a result, a transverse magnetization component is produced. Therefore, the precessing spins generate an electric current that we can measure. An important point to note is that the RF pulse can selectively influence hydrogen nuclei with a specific rate of precession (due a specific magnetic field), and this is used for spatially selective pulses or for magnetization transfer contrast, as discussed later.

When the RF pulse ends, the hydrogen nuclei begin to relax back to equilibrium, with a net magnetization parallel to B_0, and no transverse magnetization component. The process follows an exponential time course to approach the equilibrium state,

with the characteristic time to recover the longitudinal magnetization known as the longitudinal relaxation time, or T_1 (with typical values of around 0.7–2 s). The time it takes for the spins to align to B_0 (or the T_1 relaxation time) is determined by the strength of the magnetic field, the temperature inside the body, and the properties of the movement of the hydrogen nuclei within the tissue (put simply, the mobility). This will come up later in a discussion on myelin water imaging and diffusion tensor imaging. Different environments, such as water and lipids, and even different water environments with different mobility, can result in different T_1 values that provide signal contrast between tissues and can distinguish healthy and damaged tissues, for example. In addition, the transverse component of magnetization decays to zero with an exponential decay characterized by the transverse relaxation time, or T_2 (with typical values of 50–150 ms). The rates of transverse and longitudinal relaxation are quite different and depend on the tissue properties, and T_1 is typically about ten times longer than T_2 in biological tissues. The transverse component can also decay more quickly if the magnetic field is not exactly the same everywhere, resulting in a spread of precessional frequencies, and causing the nuclei to get out of phase. As a result, there is a second transverse relaxation time, T_2^*, which includes the effects of transverse relaxation as well as spatial variations in magnetic fields which are often caused by the different tissue properties in the body. For biological imaging, T_2^* (with typical values of around 20–50 ms) is much shorter than T_2. The relaxation times vary with magnetic field strength, but more importantly they are highly dependent on the tissue environment and can provide useful physiological information about the tissues. As discussed below, relaxation times can be used to influence the MR signal intensity and distinguish different tissues, or identify changes due to injury or disease.

10.3.3 Where Is the Signal Coming From?

Now that we know how we get a signal from the body that we can measure, we need to know where that signal comes from in order to create an image. To know where in the body the signal is coming from, we make the frequency and phase of the precession of the hydrogen nuclei depend on the location of the body, by using spatially dependent magnetic fields known as "gradients." This is accomplished by three spatial encoding steps. First, a slice (z) of the image is selected by applying a slice selective gradient. Essentially, applying a magnetic field gradient changes the Larmor frequency of the hydrogen spins in a position-dependent way such that the frequency depends on position. The RF pulse is applied at a specific frequency such that only a narrow range of tissue is excited (tipped from the equilibrium state). Remember that we said that RF pulse only affects the hydrogen spins at the same frequency as the pulse. Next, other gradients are applied in order to assign a specific frequency to each voxel in 2D space (x, y). This occurs by applying a gradient for a short duration, making the phases of the hydrogen nuclei depend on position (i.e., "phase encoding"), and then applying a gradient in another direction, while the MR signal is recorded, so that the frequency of precession depends on position in the

second gradient direction (i.e., "frequency encoding"). The phase and frequency encoding can be ambiguous, and so a large number of different amounts of phase encoding are applied in sequential acquisitions. By acquiring a complete set of data, we can mathematically work out where the signals originated within the slice. The hydrogen nuclei in each voxel will have a specific phase and frequency fingerprint so that when the signal is measured, we know where it came from, and we can plot the signal strength vs. position to produce an image. This process influences the time it takes to acquire a set of images, and the spatial resolution that we can obtain to detect the effects of injury or disease. With more data acquired, we can obtain higher-quality images, at the expense of more time taken.

10.3.4 Making the Image Depend on the Tissue Properties

In general, the purpose of MRI is to acquire images with contrast between tissues, so that we can identify anatomical features, detect and locate abnormalities, or even detect changes in a given tissue over time. Therefore, we need a way to make sure that our image contrast arises from the tissue properties, so that we can distinguish between gray matter and white matter or detect a hematoma from the surrounding tissue, for example. There are two key MRI parameters that determine the contrast of our images: the repetition time (TR) and the echo time (TE).

The repetition time (TR), or how long after you apply an RF pulse before you apply another one to affect the same region, determines how much recovery can occur along the longitudinal axis. The longer the TR, the more recovery time is allowed for the longitudinal magnetization (T_1). However, because the T_1 is dependent on tissue properties, different tissues have different T_1 values (the time it takes for the magnetization to recover along the longitudinal axis). If you want to distinguish between two tissues, you need to have a shorter TR so that a different amount of the magnetization has been recovered in one tissue compared to the other. If you select a very long TR, you eliminate T_1 weighting from your images because both tissues will have fully recovered their magnetization along the longitudinal axis (cannot distinguish between them).

Conversely, the time at which you measure the signal after the RF pulse is called the echo time (TE). The echo time determines how much signal is allowed to decay in the transverse plane (the signal that is measured to create the images). Long echo times mean that more of the signal has time to decay, but also that tissues with different properties that decay at different rates will have time to separate from each other in the amount their signal has decayed. Therefore, a very short TE reduces the T_2 weighting (both tissues have little signal decay), while longer echo times allow the decay rate differences in the tissues to become more apparent (one tissue will have decayed more than the other).

Intentionally setting the TR and the TE at specific values will determine the weighting, either T_1 or T_2 (or both), of your images and will influence the contrast between tissues. For example, lipids tend to have relatively short T_1 and T_2 values (~280 ms and ~85 ms respectively) [39]. In comparison, the water component of tissues can be considered as having a "free" component, which behaves essentially

like pure water and has long T_1 and T_2 values of almost 2 s, and also a "bound" component with strong interactions with macromolecules, ions, structural elements of cells, etc., and consequently very short T_2 values of <1 ms. The relaxation times observed in tissues are typically a mix of the lipid component and a water signal which is influenced by rapid exchange between the "bound" and "free" states. Therefore, if you set your TR to be long such that all tissues have recovered along the longitudinal axis and you set your TE to be long enough to distinguish the decay between the two tissues, the images will be T_2 weighted. This will result in the signal from water being greater than the signal from lipids, and water will appear bright in the image. Alternatively, using short TR and TE values can result in higher signal from the faster relaxing lipids, resulting in water appearing dark and lipids appearing bright in the image. Therefore, for clinical imaging or research, the user can be intentional in how they set the TR and TE values in order to use the T_1 and T_2 weighting properties to look for edema, hemorrhages, meningiomas, etc.

10.3.5 Echoes, Echoes, Echoes

It is important to note that the gradients we apply to encode spatial information in the MR signal cause the signal to decay very quickly, making it difficult to detect. However, we can recover the signal briefly, and measure it, by producing signal "echoes." There are two types of echoes, spin echoes and gradient echoes. In a spin echo sequence, the RF pulse is applied (90°), and after a certain amount of time (TE/2), we can apply another RF pulse with a 180° flip angle. The 180° pulse reverses the signal dephasing caused by any gradients and magnetic susceptibility effects, and the signal will come back into phase, producing a signal maximum, i.e., an "echo," at the echo time (TE). In contrast, a gradient echo is produced by applying a gradient after the initial RF pulse and then applying a second gradient in the opposite direction to reverse the effects of the first and cause a brief echo. However, the dephasing caused by magnetic susceptibility effects will not be canceled out, and the relaxation will occur much faster (T_2^*). To reiterate, either a spin echo or gradient echo can be applied to bring the hydrogen nuclei back into phase, so we can measure the signal in the presence of a magnetic field gradient. However, spin echoes are T_2 weighted, whereas gradient echoes are T_2^* weighted.

10.3.6 Bringing It All Together

With the components of the imaging process described above, we have the means to produce an MRI signal, primarily from water and lipids, and encode spatial information into the signal to produce an image. It is important as well that we have the means to weight the images according to T_1, T_2, or T_2^* (or a combination). With an understanding of the processes underlying relaxation, we can glean useful physiological information from the image signal, in addition to the anatomical detail that is depicted by the images.

10.3.7 Challenges for Imaging in the Spinal Cord

MRI of the spinal cord offers a noninvasive means of investigating the disruption of spinal cord that result from injury. However, the spinal cord environment presents additional challenges for MRI methods, beyond those encountered with brain MRI. The spinal cord is surrounded by a number of different tissues including cerebral spinal fluid, bone in vertebrae, and air-tissue interfaces due to the proximity of the lungs. These different environments have different magnetic properties, which locally change the magnetic field such that it is not homogeneous across the region you are imaging. This can lead to image distortions and a loss of spatial fidelity in the images. Furthermore, the cord is moving in the spinal canal as a result of cardiac-induced pulsatile CSF motion [10, 32]. Finally, the spinal cord has small cross-sectional dimensions, which results in partial volume effects (a mix of tissues with different relaxation properties in one voxel). Therefore, a number of adaptations have been employed in order to circumvent the limitations of imaging in the spinal cord [5, 42]. Each new advance to overcome or reduce any one of these challenges enables acquisition of better data for characterizing and overcoming other challenges.

10.3.8 MRI in the Spinal Cord

MR images, specifically T_1- and T_2-weighted images are routinely acquired in clinical practice when a spinal cord injury or disease is expected. For example, T_2-weighted images are widely used for assessing lesion number and volume in multiple sclerosis (MS). In fact, the 2010 Revisions to the McDonald Criteria for the Diagnosis of MS state that the clinician must identify "at least one T_2 lesion in at least two of four locations considered characteristic for MS" and there must be evidence of at least one "new T_2 lesion to establish dissemination of time" (DIT, which illustrates the progression of the disease) [33]. Here, "T_2 lesion" is a jargon term used to indicate a lesion identified by means of the tissue contrast in a T_2-weighted image. Typically, T_2-weighted fast spin echo (FSE) imaging is used to image in the spinal cord in suspected cases of MS, and proton density-weighted images have been shown to be informative as well [37, 43]. Weaknesses of T_2-weighted imaging of MS have been identified as being the lack of ability to discriminate demyelination, edema, inflammation, Wallerian degeneration, and axonal loss, because all produce hyperintense features in MR images [34]. A recent study [29] has shown that gradient echo images acquired in axial planes can provide better anatomical contrast. Anatomical images are also acquired to determine tumor location and size and the presence of cord compression [7]. Furthermore, the transverse area of the spinal cord (determined via anatomical images) "closely mirrors the clinical presentation of cervical spondylotic myelopathy and may be used in predicting surgical outcomes" [18]. Specifically, the transverse area of the spinal cord was shown to be strongly related to the total number of neurological signs in a patient and was correlated

with the severity of CSM on presentation and after surgery. Relaxation time-weighted images (T_1, T_2, T_2^*) make use of the relationship between relaxation times and the water and lipid environments in tissues, in order to provide insight into physiological and/or structural changes at the cellular level. MR images are therefore invaluable for the detection of disease or injury and for determining the extent or progression. Images can be assessed visually for gross morphological changes or quantitatively to provide measures of changes in structure or quantify changes in relaxation times. However, some methods that make use of the full extent of information that can be gleaned from these images require extensive calculations and image processing (such as measures of cord atrophy) and are currently limited to clinical research studies.

10.4 Functional MRI

Since the seminal 1990 paper by Ogawa describing the blood-oxygen-level-dependent (BOLD) contrast in MR images and relating blood flow to neural activity, the use of BOLD functional MRI for the study of brain function in behaving humans has revolutionized the field of neuroscience [27]. This technique enables a noninvasive, systems-level understanding of real-time neural function with relatively high spatial and temporal resolution. Functional MRI allows us to see the previously invisible; therefore it has great research and clinical potential. It has been adopted by many fields (e.g., psychology, sociology, economics, neuroscience, etc.) and has been widely applied to a number of research topics.

Functional MRI (fMRI) refers to measuring the function of neurons in response to an external task, or experimental manipulation, or cognitive state. This technique involves acquiring images exactly as described above, over time. The result is a time series of anatomical images in which subtle differences in the image intensity correspond with neural activity, albeit indirectly. The correspondence of the images to neural function is critical and arises from the different magnetic properties of oxygenated and deoxygenated blood and the relationship between blood flow and neural activity. Neuronal signaling generates an energy demand that is satiated by an oversupply of oxygenated blood and, perhaps counterintuitively, less deoxygenated blood in the region [11]. This occurs through a series of interactions between neurons, astrocytes, and blood vessels. Deoxygenated blood (specifically the iron in the hemoglobin) is paramagnetic, meaning that when it is in a strong magnetic field, a weak magnetic field is induced within it, in the same direction as the external field. It therefore alters the magnetic field around it. Oxygenated blood is diamagnetic, meaning that when it is in a strong magnetic field, it has a weak magnetic field in the opposite direction of B_0 and therefore actually works to increase the homogeneity of the local magnetic field. As a result, both T_2 and T_2^* values are increased, resulting in higher MR signal intensity in relaxation time-weighted images. This is known as the blood-oxygen-level-dependent (BOLD) contrast and is commonly used for functional MRI. It is important to note that BOLD contrast is not a direct measure of neural firing but is rather a metabolic

correlate that more closely corresponds to excitatory and inhibitory postsynaptic potentials than action potential firing [24].

Although functional MRI has been used predominantly in cortical regions, it has also been adapted for use in the spinal cord. Some modification of the methods used for cortical fMRI has been necessary because of the additional challenges faced when imaging the spinal cord, as discussed above. Nonetheless, methods have been developed that have been shown to be sensitive and reliable and have been used for a wide range of research studies [42, 46].

Currently, spinal cord fMRI is used predominantly for clinical research, as opposed to being used for clinical assessment or evaluation of spinal cord trauma. Therefore, the use of spinal cord fMRI is limited to studying groups of individuals and only general conclusions can be made regarding the gain or loss of function after trauma. Numerous studies have investigated functional reorganization in the brain after spinal cord trauma or disease [14, 15, 17, 21, 26, 36, 49, 50]. However, relatively few studies have examined the functional reorganization in the spinal cord. Of these studies, fMRI has been used as a means to investigate the sensory function post-traumatic injury [6, 40, 41]. For example, SCI patients were stimulated with thermal sensory stimuli both above (normal sensation) and below the level of their injury. The results of this study provide evidence for altered sensory processing post-traumatic injury. Spinal cord fMRI has also been used to study spinal cord damage that results from multiple sclerosis and has been used to investigate proprioceptive-associated cord activity and tactile changes and compare primary progressive and secondary MS [1, 2, 45]. These studies demonstrate how fMRI can be used as a tool to capture alteration in function or residual function in the spinal cord post injury.

For spinal cord fMRI to be used routinely as a clinical assessment tool, it must be shown to produce sensitive, reliable, and robust results for individual patients that then can be accurately interpreted. It is also important that the method is practical to use in MRI units in hospitals. Specifically, the task or sensation that the participant will engage in needs to be accessible and easy to set up. If this can be accomplished, fMRI will be a means of assessing spinal cord anatomy and function over time and may supplement current assessment measures. This technique has the potential to be important for demonstrating the efficacy of a therapeutic intervention and may provide end points in future clinical trials.

10.5 Diffusion Tensor Imaging

Diffusion tensor imaging (DTI) is an MR imaging technique that is used to examine the self-diffusion of water molecules within biological tissue. Therefore, it can provide invaluable, clinically relevant biological information regarding the compositions and architectural organization of tissues. When free diffusion occurs, molecules disperse equally in all directions, known as isotropic diffusion. However, when a physical barrier is introduced (such as myelin sheath, axonal membranes, or neurofilaments), diffusion is restricted perpendicular to the barrier resulting in anisotropic

diffusion. Capturing how much or how little the water can move/diffuse tells us a lot about the physiological environment.

Diffusion-weighted images (DWIs) are acquired similarly to anatomical MR images; however an additional "diffusion-encoding gradient" is applied to the MR sequence to sensitize the MRI signal to the displacement of the water molecules. In a DW sequence, a gradient is applied after the 90° RF pulse and causes the magnetic moments (water protons) to become out of phase. After this initial gradient is turned off, time is given for diffusion to occur before the second refocusing gradient is applied. The second gradient will reverse the phase distribution of the hydrogen nuclei and return a strong signal intensity. However, if diffusion occurs, the hydrogen nuclei will no longer be in the same spatial position along the gradient, and therefore the effects of the two gradients will not perfectly cancel out. Therefore, the measurement of the signal intensity can be used to determine the apparent diffusion coefficient in the direction of the applied gradient [3]. Diffusion-weighted imaging is therefore typically done with a number of acquisitions with diffusion encoding in different directions. In diffusion-weighted imaging, three gradients are applied in orthogonal directions, and the images are calculated as an average to obtain a mean diffusion map.

In contrast, diffusion tensor imaging (DTI) involves the measurement of diffusion in multiple directions in order to capture the direction of the diffusion, in addition to its magnitude. The direction in which the MR signal is attenuated the most (has the largest distribution of phases of the hydrogen nuclei) is the principal direction of diffusion. Greater diffusion occurs parallel to the direction of organized white matter tracts, compared to across the tract, resulting in anisotropic diffusion. The principal axis of diffusion corresponds to the predominant orientation of the cellular structures in each voxel. In comparison, gray matter does not tend to have a high degree of anisotropy, or a predominant direction of water diffusion. To fully describe the diffusion tensor, diffusion-sensitizing gradients must be applied in at least six noncollinear directions, and one non-diffusion-weighted image ($b = 0$) must be acquired for comparison. However, the more gradient-encoding diffusion directions that are sampled, the more accurately the diffusion coefficients can be calculated [30]. There are two key quantitative parameters that are calculated from DT image: mean diffusivity and fractional anisotropy (FA). Mean diffusivity is an average of the calculated eigenvalues and describes the amount of overall diffusion distance in the sample/voxel. Fractional anisotropy refers to the ratio of diffusion in different directions. Mean FA maps and colored FA maps are often seen in the literature and describe the direction of anisotropic diffusion (e.g., red indicates left/right diffusion, blue indicates superior/inferior diffusion, and green indicates anterior/posterior diffusion).

10.5.1 DTI in the Spinal Cord

Diffusion tensor imaging in the spinal cord is subject to the same challenges as the functional and anatomical imaging techniques. However, there are additional

challenges for DTI as the fast imaging sequences (typically "echo-planar imaging" (EPI)) that are used to acquire the images are extremely sensitive to magnetic field inhomogeneities which exist due to the physical environment of the cord. There have been some technological advances to circumvent these limitations, and DTI has been used to study patient groups in research settings [19, 42, 44, 46]. DTI has recently been proposed to be a useful clinical aid for defining the margins of a spinal cord tumor and also aids in determining whether the spinal cord white matter is splayed around the tumor or is infiltrated through the tumor, indicating when a biopsy is necessary [8]. DTI has also been used to investigate the effects of traumatic spinal cord injury and a significant reduction in FA values in the corticospinal tract which corresponded to impairments in upper limb function [13]. There are currently a number of clinical research applications of DTI (for a review, see [4, 46]). However, the use of DTI echoes that of fMRI in that this technique has not yet reached its clinical potential and is largely limited to clinical research studies. Although the clinical use of spinal cord DTI is forthcoming, a number of methodological improvements are still required before the full benefit of DTI can be realized in the spinal cord.

10.6 Magnetization Transfer Contrast (MTC) Imaging

Contrast between tissues with different properties, such as gray matter and white matter, can be produced by making use of the multiple relaxation environments that exchange quickly on the time scale of relaxation, as described above [25, 48]. Even though hydrogen nuclei may move between two or more relaxation environments and exchange energy between nuclei in different environments, each environment has specific properties that can be exploited. The water in hydration spheres around macromolecules and lipids relaxes very quickly because of strong interactions between adjacent nuclei and because of the altered movement of the water molecules. These interactions also create a broader spread of magnetic field intensities and therefore a broader spread of precession frequencies, than in the "free" water [25]. In general, an RF pulse will affect all of the hydrogen nuclei at (or very near) a certain frequency of precession. The hydrogen nuclei can exchange rapidly between these water components, and the net signal is a mix of the different environments. However, it is possible to use a specially designed RF excitation pulse to affect only the "bound" (wide frequency range) component and miss the "free" component. This RF pulse is typically very long, or has a specially designed shape, so that it acts on only a very narrow frequency range. The pulse also produces a very high flip angle (several full rotations) so that it "saturates" the spins. This means the spins are evenly distributed along the $\pm z$-axis and do not produce any net signal. Because hydrogen nuclei will exchange rapidly between different water components and will also exchange magnetic energy, the saturation becomes distributed throughout all of the water quite rapidly. The rate of exchange between the different water components is a key factor determining the total effect of the RF pulse, but it also depends on the relative amounts of water and the relaxation times

of each component. The amount of signal reduction that is produced is called the "magnetization transfer ratio" or "MTR," and it varies between different tissues and fluids. The effect of this frequency-selective excitation is termed "magnetization transfer contrast" (MTC), and it is particularly useful for contrasting tissues and fluids with different amounts of bound water and/or different exchange rates. For example, whereas gray matter and white matter have magnetization transfer ratios (MTR) of 40–60 %, in skeletal muscle it is 75 %, and in blood, CSF, bile, and urine, it is less than 5 %.

In the spinal cord, MTC has proven to be very useful for obtaining detailed anatomical images with good contrast between gray matter and white matter regions and changes in white matter such as with multiple sclerosis [38]. The addition of MTC does not increase the overall image acquisition time relative to the conventional gradient echo sequence, but it can significantly alter tissue contrast. MS lesions are hyperintense relative to normal appearing white matter with gradient echo (GRE), fast spin echo (FSE), and gradient echo with MTC (MT-GRE) sequences, but the contrast is greater with the GRE and MT-GRE sequences. Importantly, Ozturk et al. [29] found that the lesion load identified in MS cases was greater with GRE and MT-GRE imaging sequences, as compared to the more commonly used T_2-weighted FSE sequence, but they did not observe that MTC provided any improvement of lesion detection over conventional GRE. However, other studies have shown improved lesion detection with MTC and quantification of the magnetization transfer ratio (MTR), and detection may depend on whether lesions are in gray matter or white matter and the stage of lesion progression [12, 35].

Quantitative MTC (qMTC) methods have also been developed to determine magnetization transfer rates and therefore provide more information about tissue properties. However, there are a number of technical challenges to overcome for qMTC that are exacerbated by the environment in the spinal cord. The small cross-sectional dimensions of anatomical structures in the cord require high-resolution imaging, and problems of physiological motion and the poor magnetic field homogeneity can interfere with accurate observations of the MTC effect in the cord. In order to estimate quantitative magnetization transfer rates, a number of measurements are required, and the demands of high resolution and high signal-to-noise ratio result in very long scan times that may make this method impractical for clinical use. However, recent advances show promise at developing a quantitative MTC method that is effective for use in the human spinal cord [38].

10.7 Myelin Water Fraction (MWF) Imaging

Whereas MTC exploits the differences between the "free" and "bound" water components, another adaptation known as myelin water fraction imaging (MWF) makes use of the fact that white matter and gray matter have different contributions from these two water components. Specifically, water that has been attributed to being bound within myelin sheaths is more abundant in white matter than gray matter. In

gray matter and white matter in the brain, two predominant relaxation components are attributed to myelin water with a T_2 of around 15 ms and intracellular and extracellular water with a T_2 of approximately 80 ms [16, 47]. The myelin water fraction (MWF), which represents the fraction of tissue water bound to the myelin sheath, has been reported to be a validated marker for myelination in central nervous system tissue in vivo [22]. This method has been shown to be useful for detecting changes in myelin, such as in multiple sclerosis, and for characterizing atrophy as a result of injury or aging [23, 51].

The MWF imaging technique consists of identifying the MR signal contribution from different relaxation components, and it therefore is based on quantification of multicomponent relaxation times and relative contributions. This quantification can be challenging in human subjects because it can be very time consuming, and much of the effort to develop MWF imaging has focused on reducing acquisition times to make it practical. Two different approaches are being developed, but both require acquisition of a number of sets of images with a range of imaging parameters to vary the sensitivity to relaxation times in a systematic manner. One technique involves acquiring spin echo images over a range of echo times and has shown white matter to contain roughly 11 % of its water trapped within myelin [28, 47]. The other technique involves a combination of spoiled gradient echo imaging and steady-state gradient echo imaging with a range of flip angles for the RF excitation pulses (termed "mcDESPOT") and has been shown to provide whole-brain measurements in under 30 min [9]. More recent studies have also shown whole-brain acquisitions in about 13 min, with myelin water fractions of about 20 % in white matter in a control population and around 7–13 % in white matter lesions in patients with multiple sclerosis [20]. However, comparative studies show that that results obtained with these two methods can be very different, with considerably higher proportions of tissue water attributed to myelin with mcDESPOT [52]. From this comparison, it is suggested that the results obtained with the two methods cannot be considered to be equivalent. It appears therefore that more validation of methods for quantifying myelin water may be needed before this approach has clinical value.

10.8 Case Study

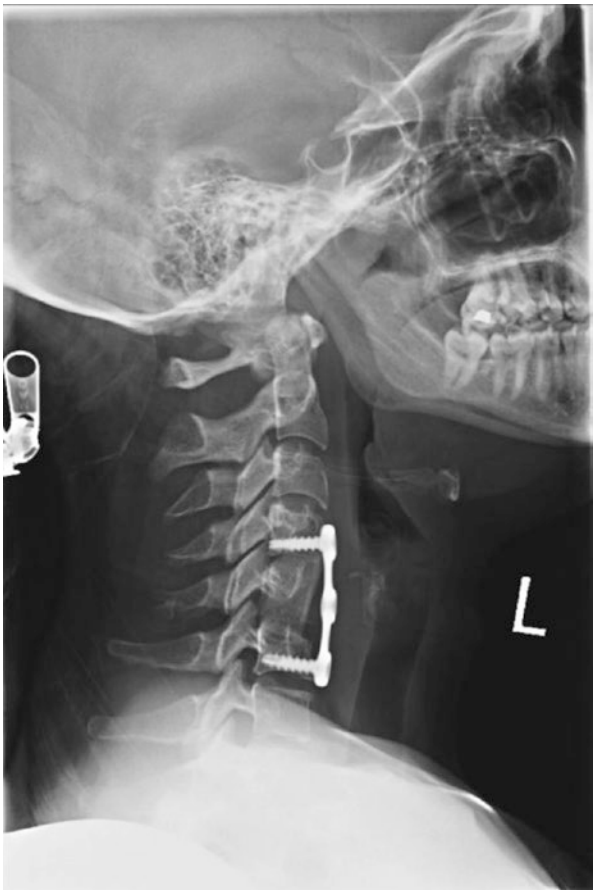
While on holidays at a friend's cottage, EH, a 23-year-old female, went swimming and dove head first into shallow water. She ruptured her C5 vertebra and the adjacent spinal cord tissue was injured. She was immediately taken to the local hospital and a series of diagnostic tests, and extensive rehabilitation, ensued. We met EH several years after the accident when we were recruiting for volunteers with traumatic spinal cord injury for an imaging study. EH agreed to participate in that study and has since volunteered for us several times and has given us permission to access to her medical images and present them here.

After arriving at the hospital, the general procedure is to have patients undergo a number of neurological clinical assessments including a patient history, general physical examination, and evaluation of neurological status. If the patient exhibits

neurological deficits, as was obvious in EH's case, cervical spine imaging is conducted. According to the American College of Radiology Appropriateness Criteria, a CT cervical spinal image without contrast is usually the first imaging procedure in the case of a suspected cervical spinal injury. X-rays of the cervical spine and MRIs of the cervical spine (without contrast) may also be appropriate, depending on the suspected damage.

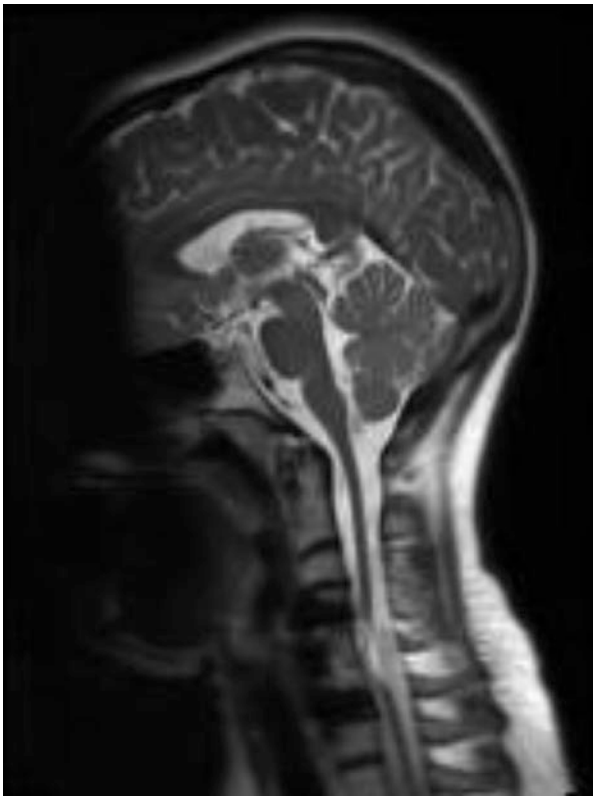
Cervical spine CTs are considered superior to plain X-rays as they are more sensitive to detect spine fractures and generally take less overall time to acquire [31]. In comparison, MRIs are used to evaluate neurological symptoms and disruption of the ligaments. Importantly, MRI can be used to visualize the spinal cord and can determine whether the cord is compressed, or if there is a hemorrhage and offers prognostic information regarding potential recovery post injury. However, these images are time consuming and expensive to acquire and have contraindications for some patients.

Examples of X-ray images, anatomical MRI, and fMRI, from EH's medical file, help to illustrate the value of each of these modalities.



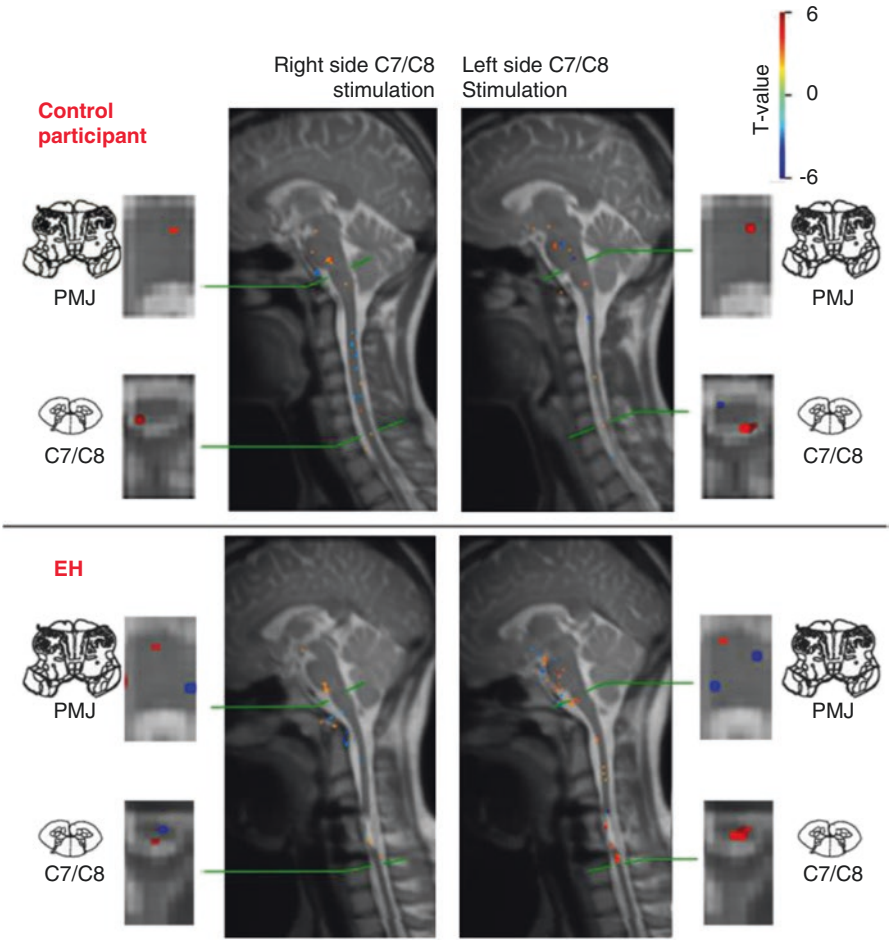
10.8.1 X-Ray Imaging

This is an X-ray image of EH post spine surgery. You can clearly see her vertebrae, as well as the metal screws and rod that were inserted between the fourth and sixth cervical vertebra to stabilize her spine. The overall goal of this surgery is to preserve or improve neurological function, provide stability, and decrease pain. The vertebrae and other bony structures are clearly depicted, whereas the spinal cord and any evidence of neurological changes are not visible.



10.8.2 Anatomical MRI

Here we show a T_2-weighted fast spin echo imaging of EH's head and neck, in a midline sagittal slice. This MRI method has low sensitivity to magnetic field distortions that are often caused by metallic spinal fixation devices. Signal voids at the positions of the screws and plate across the C4–C6 vertebrae are clearly visible. The disruption to the spinal cord tissue at the same level is also clearly demonstrated. Although the cord tissue is clearly visible and the tissue disruption is evident in this image, there is no evidence of how neurological functions have been altered by the injury.



10.8.3 Functional MRI

EH volunteered for research functional MRI studies with thermal stimulation on the right and left hands, on the little finger side of the palm, corresponding to the eighth cervical spinal cord segment, below the level of injury. The top panels show corresponding results from an age- and gender-matched person with no previous injury. Areas of the spinal cord and brainstem that responded to thermal stimulation of each hand are indicated on the anatomical images in red for positive responses and blue for negative responses. Transverse sections through the cord and brainstem are also shown for selected locations to illustrate the cross-sectional distribution of the responses detected with fMRI. These results demonstrate neural communication from below the level of injury to the brainstem, for both right-side and left-side stimulation. The activity detected on both sides is altered relative to the control

participant example, but is nonetheless present. This is one of the few techniques that can be applied noninvasively in people that can show the neurological changes in the spinal cord as a result of injury.

10.9 Summary

Routine clinical imaging primarily consists of plain film X-ray, and, if there is evidence of neurological deficit, CT is often used. MRI is less commonly used, but is known to provide important supplementary information. While X-ray-based imaging methods clearly depict disruption to the bony structures, they only give evidence for or against suspected neurological damage. MRI can demonstrate tissue damage to the spinal cord, whereas to obtain any information about neurological changes as a result of traumatic spinal cord injury, functional MRI is needed. However, current fMRI methods are entirely experimental and are useful for clinical research but have not yet reached the stage of clinical use.

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Spinal Cord Neurophysiology

11

Andreas Hug

Abstract

Neurophysiological techniques and their clinical value in a spinal cord injury (SCI) specific context are discussed in this chapter. Since spontaneous neurological recovery is much better in clinical incomplete compared to complete cases, the rational for a detailed analysis of motor and sensory pathways after SCI is based on the intention to find markers of lesional incompleteness. For this reason, neurophysiological techniques are applied to investigate parameters of connectivity (e.g., somatosensory evoked potentials (SSEPs), motor evoked potentials (MEPs)) and the impact of that connectivity (e.g., reflex studies, patterns of muscle activation in polyelectromyography).

11.1 Introduction

After spinal cord injury (SCI), patients and clinicians alike raise important questions to neurophysiologists. Some of those are (1) objectification of the clinical exam, (2) early prediction of outcome, (3) monitoring the natural course, (4) measuring treatment effects, and (5) understanding the pathophysiological and functional basis for the neurological deficit (e.g., complete/incomplete/discomplete lesions). The rational for a detailed clinical analysis of motor and sensory pathways after SCI is based on the intention to find markers of lesional incompleteness. Spontaneous neurological recovery is much better in clinical incomplete compared to complete cases [62]. Since the spinal fiber tracts are accurately (somatotopically) organized within the spinal cord, anatomically incomplete spinal cord lesions spare one or the other fiber tract function. In the clinical exam, this can be evident as (1) sacral sparing or (2) incomplete spinal cord (e.g., central cord, Brown-Séquard, or anterior cord) syndromes (see chapter 3). For the general cross-sectional somatotopic organization of the cervical spinal cord see Fig. 11.1.

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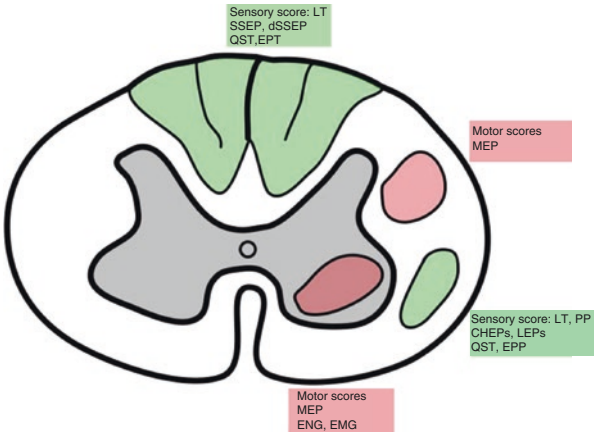

Fig. 11.1 Somatotopic organization of the spinal cord. Within white matter: green illustrates sensory and red motor fiber tracts. Within gray matter: red depicts anterior horn alpha-motoneurons. Somatotopy-specific clinical and neurophysiologic measurements are illustrated in the text boxes. *SSEPs* somatosensory evoked potentials, *dSSEPs* dermatomal somatosensory evoked potentials, *QST* quantitative sensory testing, *EPTs* electrical perception thresholds, *EPP* electrical pain perception, *MEPs* motor evoked potentials, *ENG* electroneurography, *EMG* electromyography, *LT* light touch, *PP* pinprick, *CHEPs* contact heat evoked potentials, *LEPs* laser evoked potentials

During the acute setting, clinical questions mainly focus on elementary motor (e.g., muscle strength), sensory (e.g., sensation, discrimination), and autonomic (e.g., bladder emptying) functions and the early prediction of outcome [37, 177]. In this context, neurophysiology is commonly requested not only in order to objectify the clinical exam but also to offer an even higher precision than the clinical exam alone, i.e., providing a higher sensitivity and specificity with particular respect to the completeness of the injury. Despite such understandable clinical needs, not neurophysiology but the standardized neurologic examination still represents the mainstay and "gold standard" for a meaningful clinical classification, grading, and, based on this, the prediction of outcomes after SCI [42, 69, 92, 157, 159, 170–172, 180] (see chapter 4). Compared to a structured neurologic examination according to the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) [4], no single or combined neurophysiological technique provides a better classification or prediction accuracy with respect to global or specific (e.g., ambulation) outcomes after SCI [150, 168]. Clinical classifications acutely after the SCI, i.e., >72 h after injury [15, 62, 69, 80], can sufficiently predict long-term neurological and functional outcomes, enabling physicians to tailor rehabilitation plans accordingly. Frequently, traumatic SCI is associated with concomitant injuries [75, 121, 124]. Particularly for patients with concomitant brain injury, clinical classification can be inaccurate [121]. For those situations or in, e.g., patients under sedation, neurophysiology can be a useful tool to detect neurological dysfunction as was demonstrated by, e.g., fractionated somatosensory evoked potential (SSEP) recordings [85].

With respect to the monitoring and objectification of neurological and functional recovery after SCI, conventional MEP and SSEP recordings seem to be of limited value [43, 53, 173]. However, a large longitudinal dataset suggested that clinical recovery (motor scores and ambulation) was paralleled by an increase in MEP amplitudes to the tibialis anterior muscle [135]. Furthermore, surface electromyography (EMG) recordings correlate with motor recovery [111, 123]. Dermatomal SSEPs (dSSEPs) in combination with, e.g., electrical perception threshold testing are currently under clinical investigation and might serve as suitable techniques in order to monitor segmental spontaneous recovery and potential treatment effects in the future [58, 96, 99].

Later, in subacute and chronic stages after SCI, not only elementary but also complex functional interactions of neurological systems (e.g., sensorimotor interaction during ambulation, locomotor training) are of major importance to patients and clinicians. Neurophysiology might help here, to understand basic pathophysiological mechanisms and guide locomotor rehabilitation after SCI [52, 86, 93]. In this respect the analysis of reflex studies or patterns of muscle activation might help to guide and individualize neurorehabilitation after SCI [160].

Technically, neurophysiologists focus on amenable and recordable functionality of long spinal white matter tracts (spinal pathways) after SCI specifically on (1) descending motor corticospinal tracts, (2) ascending sensory dorsal column tracts, and (3) ascending sensory spinothalamic tracts. Corresponding fiber tract-specific ISNCSCI assessments are (1) motor scores, (2) light touch sensation, and (3) pinprick sensation. Motor scores, however, do not exclusively measure the functionality of spinal motor pathways. In fact, the total central and peripheral corticomuscular pathway influences motor scores. Similarly, sensory scores are influenced by parts of the peripheral and central nervous system and not only by the spinal cord lesion. In clinical routine, several neurophysiological techniques exist to measure (1) corticomuscular (transcranial magnetic stimulation (TMS)), (2) somatosensory (somatosensory evoked potentials (SSEP)), and (3) spinothalamic (laser evoked potentials (LEPs), contact heat evoked potentials (CHEPs)) pathways. In addition to these global (i.e., not spinal pathway specific) neurophysiological assessments, it is technically possible to identify afflicted peripheral or central parts of the nervous system by the proper selection of stimulation-recording montages. Neurophysiological techniques and their clinical value in a SCI-specific context are discussed in this chapter. As pointed out for the clinical exam, neurophysiology is intended to detect evidence for motor/sensory/autonomic incompleteness with a particular focus on subjectively unbiased recordable evidence.

11.2 Motor Evoked Potentials (MEPs)

MEPs are muscle responses evoked by transcranial electrical (TES) or magnetic stimulation (TMS) of cerebral motor neurons in order to analyze the total corticomuscular pathway [5–7, 28, 72, 125]. Within the motor cortex, TMS directly and

indirectly (transsynaptically) stimulates a subpopulation, mainly large-diameter, fast-conducting corticospinal fibers, which make direct monosynaptic contacts with spinal alpha-motoneurons. After stimulation of the motor cortex, muscular responses can be recorded as compound muscle action potentials over muscles of clinical interest. TMS has been widely adopted in clinical routine because the cortical stimuli are painless and the method is clinically helpful in a number of neurological disorders [50]. With a combination of both, TMS and a peripheral motor nerve conduction study to measure the peripheral motor conduction time (PMCT) calculations of the central motor conduction time (CMCT) are possible. PMCT can be approximated by two neurophysiological methods:

- Magnetic spinal nerve root stimulation
- *F*-wave recording: $\mathrm{PMCT} = (F + M - 1)/2$ (this method is only feasible for distal muscles)

CMCT is then calculated as the difference of the corticomuscular latency and the PMCT.

MEPs are routinely analyzed with respect to potential latencies in milliseconds and amplitudes in millivolts. Another parameter is the resting motor threshold, measured in % of the stimulators maximum output, at which at least 50 % of muscular responses with amplitudes of at least 50 μV occur. Compared to rest, a voluntary contraction of the target muscle substantially enhances its response to magnetic brain stimulation and reduces latencies (facilitation) [81]. Moreover, the variability of latencies and amplitudes is much less during facilitation. In general, latencies are less variable compared to amplitudes [28, 127]. In clinical routine, therefore, latencies during facilitation are the preferred and most accurate readout parameter in MEP recordings.

In incomplete SCI, MEPs to muscles below the lesion level usually have prolonged latencies, reduced amplitudes, increased resting motor thresholds, and impaired facilitation [14, 19, 45, 46, 70].

There is some evidence that in upper extremities despite a complete loss of voluntary muscle function, MEPs can be elicited, which might argue for a clinical complete, however subclinically incomplete, lesion [70]. Another MEP approach to uncover incompleteness is the attempt to modulate spinal reflexes below the neurological level (e.g., subthreshold flexor reflex H-reflex stimuli) by brain stimulation [76, 77, 175]. For an analysis of discomplete lesions with other techniques than MEP recording, see Sect. 11.6 [153]. Furthermore, after SCI the cortical representation of muscles changes which can be mapped by TMS [109, 163].

Patients with absent leg muscle function do usually have a loss of MEPs to the leg muscles in the very acute phase (within 6 h post-injury, spinal shock phase) [118] and also in later phases [19, 26, 29, 135]. For the prediction of 6-week motor recovery an ultra-early MEP investigation within 6 h after injury appears to be unsuitable, since no correlation with later muscle function was found. Only in already clinically apparent, voluntarily contracting muscles, MEPs could be evoked [118]. In later stages however, e.g., 1 month post-injury, patients with preserved

normal MEP latencies to both the quadriceps femoris and tibialis anterior muscles do achieve a full ambulatory function defined as no or little disturbance in walking (for the definition of ambulatory function, see [31, 39, 88]).

Over a 1-year course after SCI, MEP latencies in incomplete SCI were usually stable and thereby unsuitable for monitoring of spontaneous recovery. However, in a subgroup of patients with initially (within 15 days) recordable but delayed MEPs to the tibialis anterior muscle, latencies shortened (38.56 ± 3.77 vs. 35.4 ± 6.08 ms) and amplitudes increased (0.68 ± 0.63 vs. 1.32 ± 0.92 mV) over the 1-year course, and these changes correlated with improvements of lower extremity motor scores (13.2 ± 7.3 vs. 23.2 ± 2.6) and walking function as measured by the 10 m walking test (0.55 ± 0.66 vs. 0.86 ± 0.99 m/s) [135]. Therefore, in certain subgroups of incomplete SCI, MEP to the tibialis anterior muscle might be of value as a subclinical measure of spontaneous recovery or even as additional outcome measure for treatment effects. However, it remains uncertain if MEP changes add value to the examination of motor scores or walking function alone.

In incomplete SCI, MEPs to the abductor digiti minimi muscle in the acute phase were shown to predict hand function at around 6 months post-injury [39]. In this study, hand function was defined on an ordinal scale from 0 to 2 (0 = no function; 1 = active wrist extension with passive grasp via tenodesis effect; 2 = active grasping including intrinsic hand muscles). A loss of MEPs to the abductor digiti minimi muscles measured at a median of 25 days post-injury was associated with a failure to recover active grasping in 90 % of patients. If this prediction quality is better or independent from motor score analysis alone remains uncertain.

MEPs were also applied in order to uncover subclinical treatment effects in interventional clinical trials [78, 137, 162, 174]. In this respect, however, the clinical meaningfulness of standard MEP recordings remains to be established.

11.3 Somatosensory Evoked Potentials (SSEPs)

It is long known (around the 1950s) that afferent volleys to the cerebral cortex can be recorded after electrical stimulation of the median or ulnar nerves at the wrist [47, 48]. SSEPs can be used to evaluate both somatosensory pathways of the peripheral and the central (i.e., spinal, subcortical, cortical level) nervous system. The examined somatosensory part of the nervous system depends on the selection of (1) the stimulation and (2) the recording sites. Depending on the neurophysiological equipment (number of recording channels) multiple recording sites can be analyzed. Such fractionated analyses are also feasible in SCI patients with a supraspinally isolated spinal cord and even during the spinal shock phase [151]. SSEPs can be evoked from almost any nerve. In clinical routine, however, standardized stimulation-recording montages for tibial, median, ulnar, or pudendal nerves are usually applied [32, 120]. The somatosensory evoked potentials are usually analyzed with respect to early potential component latencies in milliseconds and amplitudes in microvolts. In relation to a standardized clinical exam, tibial nerve SSEPs correlate well with light touch scores, i.e., the dorsal column function, and poorly with pain

perception, i.e., spinothalamic function [10]. Higher stimulation intensities lead to more reliable cortical tibial nerve SSEPs after SCI [9].

Already in the acute stage, within 1–2 weeks after SCI, SSEP recording is feasible and can be clinically meaningful [27, 94, 179]. An absence of cortically evoked tibial nerve SSEP in the acute setting correlates with the clinical completeness of SCI. Furthermore, abolished cortical SSEP from any stimulation site in the acute stage are associated with poor neurological recovery. Several investigators studied the capacity of SSEP recordings as early predictors for ambulatory function [31, 36, 110, 142, 161]. Whereas agreement exists for the predictive value of absent cortical SSEP for poor neurological outcome, the value of preserved but pathologic SSEPs for good outcome is less clear. In one study the preservation or an early (within 1 week) return of tibial nerve SSEPs was associated with a favorable prognosis with respect to ambulatory function after a median follow-up of 12 months [142]. In another study a positive correlation of preserved acute-stage (within 2 weeks) cortical tibial or pudendal nerve SSEPs with 6-month ambulation was observed (ambulation defined on an ordinal scale: 0 = no, 1 = therapeutic, 2 = functional, 3 = full ambulation; for a detailed definition, see [31, 88]). This correlation was true for both, SSEPs measured on a continuous scale (latencies/amplitudes) and on an ordinal scale [36]. Ordinal scaling might be preferred over continuous scaling since clinical interpretation is more straightforward (1 = absent SSEP, 2 = delayed latency and reduced amplitude, 3 = delayed latency and normal amplitude, 4 = normal latency and reduced amplitude, 5 = normal latency and normal amplitude; see Fig. 11.2) [94]. Full ambulation defined as no or little disturbance in walking was achieved in 83 % of patients with preserved SSEP of types 4 and 5, whereas in patients of SSEP types 2–3 only 10 % and in patients of type 1 no patient achieved full ambulation. In a further analysis to predict 6-month ambulation measured by walking index for spinal cord injury (WISCI II) and 6 min walk test (6MWT) in subjects with motor incomplete SCI (ASIA Impairment Scale (AIS) C or D), lower extremity motor scores measured within 16–40 days after injury were the strongest predictor for ambulation 6 months after injury. In tetraparetic subjects, a combination of lower extremity motor scores and cortical tibial nerve SSEPs (if not symmetrical, then of the worse leg) compared to lower motor extremity scores alone improved prediction accuracy slightly (90 versus 92 % correct classifications) [181]. If such a small improvement of prediction accuracy is clinically meaningful remains to be established.

It was stated that despite neurological improvement, cortical SSEP latencies in incomplete SCI do not significantly change over a 1-year course after SCI compared to the initial exam during the acute stage. And it was concluded that this finding might argue for neural plasticity as the more likely underlying repair mechanism compared to axonal regeneration/remyelination [43]. In a further detailed analysis of the 1-year time course (within 15 days vs. 1 year) of cortical tibial nerve SSEPs, however, a certain subgroup of incomplete patients with recordable cortical tibial nerve SSEPs showed shortening of latencies (52.1 ± 1.0 vs. 48.9 ± 0.1 ms) and increase of amplitudes (0.8 ± 0.2 vs. 1.3 ± 0.2 μV). Moreover, these changes were paralleled by an improvement of light touch scores (1.3 ± 0.1 vs. 1.5 ± 0.1) and walking function as measured by the 10MWT (43.1 ± 8.1 at 1 month vs. 17.7 ± 6.5 s)

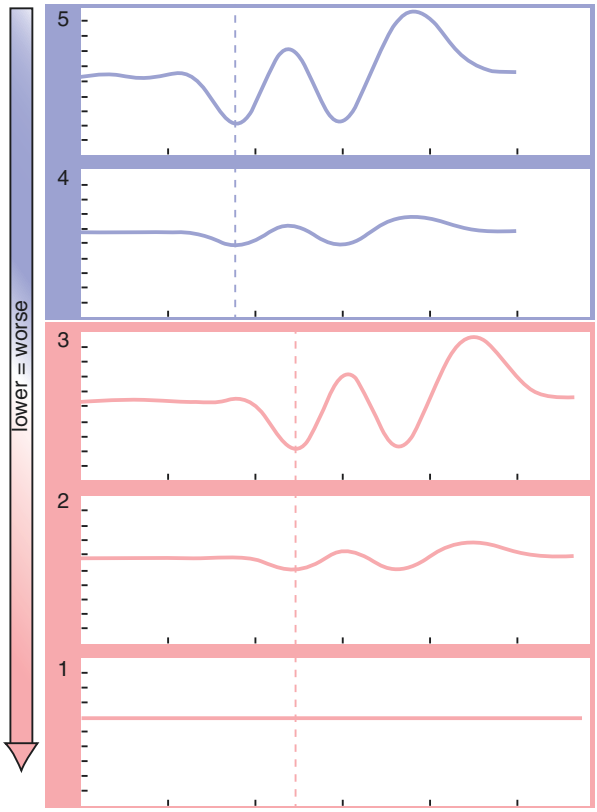

Fig. 11.2 Principle of the SSEP classification according to Kovindha and Mahachai [94] using tibial nerve SSEP as an example. Latency in milliseconds on the horizontal axis. Amplitude in μVolts on the vertical axis. *Dashed vertical lines* indicate the latencies of P40. SSEPs are classified on an ordinal scale where lower values are worse. (*1*) Abolished SSEP, (*2*) prolonged latencies and reduced amplitudes, (*3*) prolonged latencies and normal amplitudes, (*4*) normal latencies and reduced amplitudes, and (*5*) normal latencies and amplitudes. SSEPs with normal latencies are depicted with a *blue* background. SSEPs with prolonged latencies or abolished potentials are depicted with a *red* background. Such categorization was, e.g., applied in the work of [36] in order to predict outcome

[156]. Hence, for certain subgroups of incomplete patients, cortical tibial nerve SSEPs might be useful for the monitoring of spontaneous recovery or for the analysis of treatment effects. However, it remains an unanswered question, whether tibial nerve SSEP analysis adds value to the analysis of light touch scores or walking function alone.

Ordinal-scaled (five categories as described above for tibial nerve SSEPs [94]) pathological cortical ulnar nerve SSEPs measured 1 month after cervical SCI are of value as a predictor for active hand function at 6 months after injury (0 = no function, 1 = active wrist extension with passive grasp via tenodesis effect; 2 = active grasping including intrinsic hand muscles; 3 = normal or only mildly disturbed hand function) [35]. More precisely, in patients with ulnar nerve SSEP categories 1–3,

i.e., prolongation or loss of ulnar nerve SSEP at 1 month, 96 % remained with an inactive hand function (hand function categories 0–1) at 6 months. The positive predictive value of ulnar nerve SSEPs at 1 month however is quite imprecise. Only 48 % of patients with normal ulnar nerve SSEP latencies developed active or normal hand function. Slightly more accurate as a positive predictor for active or normal hand function performed cortical median nerve SSEPs, as 72 % of normal latency patients developed active or normal hand function. Another detailed study on the longitudinal evolution of cortical ulnar nerve SSEP over a 1-year period after cervical SCI corroborated the predictive value of preserved cortical ulnar nerve SSEPs within 1 month after injury for the prediction of hand function as measured by the SCIM subitem "feeding" [24, 25] at 1 year [104].

With respect to the recovery of urinary bladder function, the predictive values of cortical tibial/pudendal nerve SSEPs were investigated [41]. SSEP recordings were performed on average of 10 days after SCI and were categorized according to Kovindha et al. [94]. As outcome at 6 months, two measures were analyzed: (1) classification according to the urodynamic examination and (2) classification according to the function of the external urethral sphincter (1 = normal voluntary contraction, sensory, and detrusor function; 2 = impaired, i.e., preserved voluntary contraction and disturbed micturition due to impaired sensory and/or detrusor function; 3 = absence of function, i.e., loss of voluntary contraction and impaired sensory/detrusor function). In tetraplegic patients cortical pudendal nerve SSEPs were not clearly associated with bladder function. However, 20 % of cortical pudendal nerve SSEPs were not recordable, and this was interpreted as false-negative results as they were expected to be present. Cortical tibial nerve SSEPs were associated with 6-month outcome of both urodynamic and external urethral sphincter functions. All tetraplegic patients with normal cortical tibial nerve SSEP latencies (categories 4–5) and all paraplegic patients with normal cortical pudendal nerve SSEP latencies (categories 4–5) developed a normal bladder function as measured by the external urethral sphincter classification at 6 months. For SSEP categories 1–3, i.e., prolongation or absence of the SSEPs, the development of a normal bladder function as measured by the external urethral sphincter classification at 6 months was basically null for paraplegics and very unlikely in tetraplegics.

The diagnostic and prognostic value of cortical tibial nerve SSEP recorded at the lumbosacral level (lumbosacral evoked potentials [55, 107]) with particular respect to the differentiation between a hyper-reflexive and acontractile detrusor function is not fully clear yet. Urodynamic examinations are the diagnostic mainstay for this highly relevant and prevalent clinical question [11, 116].

11.4 Nerve Conduction Studies (NCSs) and Electromyography (EMG)

Motor nerve conduction studies of median, ulnar, radial, and peroneal nerves and sensory nerve conduction studies have been introduced into the clinical routine over 60 years ago in the middle of the twentieth century [48, 71, 83]. Even further back

(the 1930s) dates the clinical application of needle electromyography [49, 113] with major contributions later on in the 1940s/1950s [16, 17, 102, 103]. Guidelines for a proper conduct of NCS/EMG in the clinical context have been published [13, 23, 158]. Applying transcutaneous bipolar electrical stimulation to peripheral nerves, time-related motor and/or sensory responses can be evoked and recorded. Registration can routinely be performed using skin surface electrodes. For motor nerve conduction studies, the evoked compound muscle action potentials (CMAPs) after supramaximal nerve stimulation are analyzed. For sensory nerve conduction studies, the ortho- or antidromically evoked sensory nerve action potentials (SNAP) are investigated. Latencies and stimulation-recording site distances are used to calculate conduction velocities in meter/s. Potential amplitudes in millivolt (CMAP) and microvolt (SNAP) are used to interpret axonal damage to peripheral nerves. In motor nerve conduction studies, not only the direct *M*-responses but also late muscle responses like *F*-waves and H-reflexes can be elicited in order to investigate more proximal parts of the peripheral nerves (i.e., proximal to the utmost amenable proximal simulation site). Using needle EMG, one can determine acute and/or chronic neurogenic changes of innervating nerves of the respective muscles.

In the clinical context of SCI, the mentioned studies can help to detect additional nerve root or peripheral nerve injuries [8, 20, 68]. Moreover, electroneurography (ENG) assessment of peripheral arm nerves in combination with the knowledge of the spinal segmental innervation can help to infer intramedullary alpha-motoneuron damage and hereby predict the recovery of hand function in tetraplegics with lesion levels between C6 and T1 [34]. In this study hand function was defined as (1) "active hand" where the patients were at least able to use two kinds of handgrips (the pulp pinch and the lateral pinch) and (2) "inactive hand" where patients were unable to perform those handgrips. Motor ENG assessments of ulnar and median nerves were graded on an ordinal scale from 1 to 4 (1 = no CMAP (complete Wallerian degeneration); 2 = reduction of CMAP and conduction velocity (severe axonal neuronopathy); 3 = reduction of CMAP an normal conduction velocity (mild axonal neuronopathy); 4 = normal CMAP and conduction velocity). ENG measurements were performed during the first 2 weeks post-injury. Hand function (active hand vs. inactive hand) was analyzed 3 months post-injury. 90 % of hands in the ENG groups 3–4 (mild axonal neuronopathy or normal) recovered active hand function, whereas only 35 % of hands in ENG groups 1–2 (complete Wallerian degeneration or severe axonal neuronopathy) recovered active hand function. All hands of ENG groups 1–2 for both median and ulnar nerve remained inactive.

For caudal spinal cord lesions, ENG might help to discern central (epiconal) and peripheral (conal/cauda equina) nerve damage after Wallerian degeneration and consecutive CMAP reductions of tibial and peroneal nerves. Hereby it was also possible to quantitatively assess the extent of the conus/cauda lesions [144]. Severe axonal lesions at the thoracolumbar level are associated with a poor prognosis for recovery of ambulation [87, 132].

In chronic SCI ENG/EMG studies might help to diagnose secondary nerve disorders like entrapment syndromes (e.g., carpal tunnel syndrome, common peroneal

pressure palsy) [131]. Moreover, secondary damage to the peripheral nervous system below the SCI lesion level can be assessed [89, 91, 112, 166].

F-waves are late muscle responses evoked by a supramaximal antidromic electrical stimulus to a peripheral motor nerve, which occur several milliseconds after the *M*-response [57, 126]. The term *F*-waves dates back to 1950 when recordings were firstly performed from the small intrinsic muscles of the foot [119]. *F*-waves are much smaller, usually <5 % in amplitude, compared to the corresponding *M*-responses. They are believed to be generated by an echoing bioelectrical impulse in axons of alpha-motoneurons. After a distal supramaximal stimulation of a motor nerve, the antidromic conduction wave reactivates a small pool of anterior horn cells once arrived at their axon hillocks within the spinal cord causing an orthodromic conduction wave in a small number of alpha-motoneurons back to the muscles. Absent *F*-waves indicate a reduced excitability (such as hyperpolarization) of spinal anterior horn motoneurons. There is a clear temporal correlation of abolished *F*-waves with the duration of spinal shock [38, 82]. Furthermore, *F*-wave chronodispersion, i.e., the difference between the minimal and maximal *F*-wave latency, might serve as an indicator for anterior horn excitability with increased chronodispersion in SCI patients with spasticity [164].

H-reflexes are late muscle responses to transcutaneous electrical stimulation of a mixed/motor nerve [18, 67, 84]. The clinically most widely performed H-reflex of the soleus muscle is basically the electrically provoked monosynaptic Achilles tendon tap reflex (stretch reflex). Anatomically, the reflex is organized as a monosynaptic arc of afferent (Ia fibers), spinal segmental, and efferent pathways (segmental reflex pathway). The recorded response is dependent on the stimulus intensity. Submaximal electrical stimuli provoke the response when there is still no *M*-response. With increasing stimulus intensity, the *M*-response amplitude increases and the H-reflex amplitude diminishes. Supramaximal stimuli lead to a disappearance of the H-reflex.

H-reflexes can be generated even in spinal shock, a stage early after trauma characterized by a profound depression of spinal reflex activity, when tendon tap reflexes are still absent [51, 114]. The discrepancy between the presence of an H-reflex and the absence of tendon reflexes might best be explained by a reduced excitability of gamma-motoneurons which drive fusimotor activity [82] or the more complete and synchronous volley of afferent input provided with electrical stimulation relative to mechanical stimulation. Compared to flaccid spinal cord injuries, spasticity seems to be associated with increased H-reflex amplitudes [161]. However, in another study on chronic SCI, H-reflex characteristics were not different compared to able-bodied persons [148]. Since intrathecal treatment of spasticity with baclofen reduces H-reflex amplitudes, H-reflex recordings might be helpful in monitoring antispastic treatment effects in patients with SCI [117].

Bulbocavernosus and anal reflex: These reflexes are summarized here, since recording techniques are comparable to CMAP analysis in ENG recordings. Both reflexes are polysynaptic spinal reflexes at the sacral level, which can be provoked by sensory (e.g., tactile/electrical) stimuli to the penis/clitoris and perianal region, respectively.

The reflex arc of the bulbocavernosus reflex consists of sensory afferents of the pudendal nerve, spinal neurons of the sacral segments S2–S4, and motor efferents of the pudendal nerve. Different methods exist to provoke and record the reflex (e.g., mechanical stimulus and visual/tactile recording, mechanical stimulus and electrical recording, electrical stimulus and recording). For an accurate assessment of latencies and amplitudes, however, an electrical stimulus and needle/surface EMG recording montage are required. If side differences are anticipated, a needle approach is necessary [2, 3, 56, 143, 155]. The bulbocavernosus reflex is one of the first recovering spinal reflexes after SCI and can already be elicited in spinal shock. Hence, in the clinical context of acute SCI, the loss of the bulbocavernosus reflex indicates a conus medullaris or cauda equina lesion [130]. Not only in the acute setting but also in later stages after cauda equina lesions the bulbocavernosus reflex remains absent or pathologic [61].

Generally, an abolished bulbocavernosus reflex is associated with a urinary bladder dysfunction of the lower motor neuron type. Despite similarities in the neurological pathway for the activation of the bulbocavernosus and external urethral sphincter muscles [134], exact urodynamic characteristics cannot be predicted by the presence or absence of the bulbocavernosus reflex [115, 152].

The presence of a bulbocavernosus reflex in chronic male SCI patients might be of value for the selection of an ejaculation method (i.e., penile vibratory stimulation versus others like electroejaculation) [12].

The anal reflex [141] can be provoked mechanically or electrically by stimulation of the anal mucosa or the perianal skin. Electrical stimulation paradigms of, e.g., the tibial nerve, which are sufficient to provoke flexor reflexes, can also provoke an anal reflex [133]. Standardized methods for the electrical stimulation and electromyographic recording of this reflex have been described [133]. Such a standardized technique is necessary since mechanical stimulation and visual recording is insufficient to consistently elicit this reflex [1, 128]. Conditional on an intact reflex arc after SCI (i.e., cauda equina and conus medullaris need to be intact), the anal reflex can already be evoked in spinal shock [133, 139]. Hence, the loss of this reflex after SCI is associated with a conus medullaris or cauda equina lesion. The neurological pathways for an activation of the external anal sphincter and the external urethral sphincter seem to be different. Hence, a dysfunction of the external anal sphincter is not necessarily associated with a dysfunction in the external urethral sphincter. Analyses in this respect can only be done sufficiently via simultaneous pelvic floor/sphincter ani EMG during urodynamics [95, 176].

11.5 Autonomic Studies

The sympathetic skin response (SSR) is a measurement of sudomotor induced resistance changes in response to arousal stimuli, which can be, e.g., acoustic or somatosensory [30, 105, 129]. In clinical routine a standardized electrical stimulus to, e.g.,

the median nerve is utilized. For patients with high cervical SCI who are not able to perceive a median nerve stimulus, a nerve above the level of injury, e.g., the supraorbital nerve, is preferred [21, 178]. With respect to recording, sympathetic outflow to the sudomotor sweat gland of hands, feet, and the perineal region can be analyzed. The SSR gives an indication of how well the connections from the brain to the sympathetic nervous system in the thoracolumbar (Th1-L2) spinal cord are preserved. Depending on the SCI level and completeness, SSRs can be missing completely or partially. In complete cervical SCI, the SSR to hands, feet, and perineum is usually missing, whereas these responses are preserved in lesions below L2 [21, 44, 140]. Absent SSRs have been shown to be associated with autonomic dysreflexia [40, 44].

With respect to the stimulation site (i.e., stimulation below the neurological level), one interesting finding is that even in complete cervical or thoracic lesions (above L1/not cauda equina), plantar SSRs can be evoked after electrical stimulation of the pudendal nerve (approx. spinal segment S3) [138]. Since the lumbar and sacral spinal cord needs to be intact for the SSR to be evoked, these findings might argue for a sympathetic sacrolumbar spinal reflex circuit, which is independent from supraspinal sympathetic outflow. Stimulation of the tibial nerve (approx. spinal segment S1) was insufficient to evoke plantar SSRs. This is in line with the finding that increased intravesical pressures during cystometry lead to skin responses below the lesion in complete SCI patients [136].

Following electrical stimulation of the median nerve, a selective perineal SSR loss (with preservation to hands and feet) is indicative for a thoracolumbar Th10-L2 sympathetic spinal lesion and strongly associated with bladder neck incompetence/dysfunction after SCI [140]. After electrical stimulation of the median nerve or TMS, the absence of hand and feet SSR was associated with both autonomic dysreflexia and detrusor sphincter dyssynergia in cervical SCI. In thoracic SCI SSR absence to hand and feet was associated with detrusor sphincter dyssynergia but not with autonomic dysreflexia [149].

11.6 Other Methods

Routine SSEP and MEP recordings basically represent a global "longitudinal" assessment of spinal white matter tracts. However, sensitivity in order to detect changes at the segmental level is usually poor. Hence, more sensitive but still specific segmental tests are needed. For this purpose, dermatomal SSEPs, analysis of electrical perception threshold (EPT), and electrical pain perception (EPP) are currently under clinical investigation [59, 90, 96, 99, 106, 108, 145, 147, 167, 169]. Moreover, segmental MEP recordings at the thoracic level from the erector spinae muscle might improve outcome assessment in "ISNCSCI-blind" thoracic motor levels [22, 60]. Such segmental approaches might be of particular clinical importance as outcome measures in clinical trials with putatively small treatment effects [73].

With respect to sensory assessment, additional neurophysiological techniques in order to identify spinothalamic tract dysfunction (e.g., cortical contact heat evoked

potentials (CHEPs), laser evoked potentials (LEPs), quantitative sensory testing (QST)) might offer new insights, particularly in the field of neuropathic pain. These methods are under investigation and might proof more sensitive compared to the ISNCSCI "impaired" dermatome classification [33, 63–66, 74, 79, 97, 98, 100, 101, 146, 165]. One problem with CHEPs and LEPs however is that dephasing/desynchronization of afferent impulses makes it difficult to evoke cortical responses from long pathways (e.g., from the trunk and legs).

Regarding a deeper analysis of clinical complete SCI, routine SSEP and MEP recordings are of limited sensitivity. In this context, some specialized analyses of "discompleteness" were suggested [54, 122, 153]. The technical neurophysiological basis for these analyses is a brain motor control assessment (BMCA). This technique quantitatively analyzes the central nervous system control over spinal motor output [154]. The practical applicability to clinical routine and its meaningfulness for clinical routine have yet to be determined.

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Part IV

Neurological Complications

Diagnostics and Treatment of Pain in Spinal Cord Injury

12

Steffen Franz and Nanna Brix Finnerup

Abstract

Pain has various manifestations in spinal cord injury (SCI) that depend on multiple factors such as the affected tissue. Neuropathic pain is common, and nociceptive pain is frequently seen as a consequence of complications like overstraining of joints or bowel dysfunction and mainly presents as musculoskeletal and/or visceral pain.

Both, peripheral neuropathic pain, as a result of lesions to nerve roots, and central neuropathic pain, due to lesions of the spinal cord occur in SCI. It is classified as at-level or below-level pain. Neuropathic pain, which is not or indirectly related to SCI, such as carpal tunnel syndrome, is termed "other" neuropathic pain. There is limited knowledge of the underlying mechanisms in SCI-related neuropathic pain. It often develops into a chronic condition, having a crucial impact on the patients' quality of life.

Therapy of neuropathic pain includes antidepressants and anticonvulsants. Some patients experience insufficient pain relief and may experience undesirable side effects. Promising non-pharmacological therapeutic approaches beyond psychological support/therapy, like neurostimulation, are being investigated.

For treatment of nociceptive pain, it is important to identify the underlying causes and to tailor the treatment individually. Its therapy may involve different approaches comprising physiotherapy, medical treatment, including spasmolytic drugs, as well as interventional treatment.

This chapter will focus on the most relevant aspects of SCI-related pain, including epidemiology, impact on physical and psychosocial functioning, potentially underlying mechanisms, and important diagnostics. We will discuss the latest scientific knowledge and discuss the prediction, prevention, and treatment of pain in SCI.

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12.1 Background

Pain is one of the most challenging complications of spinal cord injury (SCI), with serious consequences for the patients [1–3]. Once pain has developed, it has a long-term negative impact on the patients' quality of life [3, 4]. The onset of pain is usually within the first year after the injury. The pain frequently increases over time, and more than 50 % of SCI patients develop chronic pain during the course of disease [5, 6]. Three to five years following injury, musculoskeletal pain is present in about 60 % and neuropathic pain in 50–60 % of SCI patients [7, 8]. Depending on the study design and based on considerable heterogeneity in assessing pain in SCI, its prevalence is reported with a wide variance between 26 and 96 % [9, 10]. Patients suffering from cauda equina lesions more frequently complain of severe pain compared with paraplegic patients having a thoracic level of injury or tetraplegic patients [11–13]. Nevertheless, the predictive relevance of aspects such as the level or completeness of injury is still the subject of discussion, especially in neuropathic pain types [7, 10].

12.2 Characterization and Classification of Pain Following SCI

Pain has different qualities or descriptors. The word "aching" is commonly used to describe musculoskeletal pain, whereas "burning" is typically associated with neuropathic pain [11, 14–16]. Nevertheless, this approach is not enough to capture the complex nature of the pain presentation in SCI and cannot be used to differentiate between nociceptive and neuropathic pain, especially since nociceptive pain is represented not only by musculoskeletal but also by visceral pain and other pain subtypes. Furthermore, an overlapping of different pain types and subtypes in SCI patients is a common phenomenon [17–19]. Meanwhile, numerous diagnostic tools have been developed, including questionnaires, physical examination, or even instrument-based tools, addressing a more sophisticated and accurate evaluation of the different pain types (for details please see Sect. 13.5).

Recently, an international consensus classification of pain after SCI "the International Spinal Cord Injury Pain (ISCIP) Classification" was published [20, 21]. The classification is based on three tiers: "pain type," "pain subtype," and "pain source" or "pathology," respectively (Table 12.1). The first tier classifies pain into nociceptive, neuropathic, other, and unknown pain. Other pain is pain that cannot be classified into the categories nociceptive or neuropathic, e.g., irritable bowel syndrome or fibromyalgia. In contrast, unknown pain can neither be assigned to any of the above-listed categories nor be related to a specific pain syndrome. The second tier subdivides nociceptive pain into musculoskeletal, visceral, and other nociceptive pain, and neuropathic pain into SCI-related pain (at level or below level) and other neuropathic pain. Possible underlying causes of all subtypes of pain are accordingly summarized within the third tier.

Table 12.1 The International Spinal Cord Injury Pain (ISCIP) Classification [23]

Tier 1	Tier 2	Tier 3
Nociceptive pain	Musculoskeletal pain	*For example* Articular trouble/joint pain Fracture-associated pain Spasm-related muscle pain Back pain/lumbago Pain related to heterotopic ossification
	Visceral pain	*For example* Angina pectoris Constipation/ileus Cystitis/pyelonephritis
	Other nociceptive pain	*For example* Pressure sore-related pain General wound pain Headache due to migraine or autonomic dysreflexia
Neuropathic pain	SCI-related pain	*For example* Spinal cord contusion/compression Spinal ischemia Nerve root compression Cauda equina compression
	At-level SCI pain	
	Below-level SCI pain	
	Other neuropathic pain	*For example* Brachial plexus injury Entrapment syndromes (i.e., carpal tunnel syndrome, ulnar nerve entrapment) Generalized nerve damages (i.e., metabolic nerve damages, inflammatory polyneuropathies)
Other pain		*For example* Fibromyalgia Complex regional pain syndrome (CRPS)
Unknown pain	Pain that can neither be assigned to any of the above-listed categories nor be related to a specific pain syndrome	

12.3 Nociceptive Pain

Painful stimuli to body tissue, whether mechanical, thermal, or caused by ongoing pathological processes within specific organ structures (e.g., inflammation), activate nociceptors and generate nociceptive pain. For a detailed overview of the neurobiology of pain and peripheral mechanisms of cutaneous nociception in particular, please see [22].

12.3.1 Clinical Characteristics of Nociceptive Pain

Nociceptive pain is the most frequent type of pain in individuals with SCI [7]. It is possible to differentiate between the types of pain by determining pain quality/

characteristic, distribution, clinical course, and responsiveness to any therapeutic approach. Nociceptive pain may respond well to a variety of different therapy strategies including surgical/interventional, pharmacological, and physical therapy. Its etiology can be assigned to three different subtypes:

1. *Musculoskeletal pain* is a leading cause of nociceptive pain in the chronic phase of SCI. It is described as either above, at, or below the neurological level of injury, i.e., the most caudal segment with fully preserved neurological function [23]. This type of pain has various causes and thus could accrue from overuse of joints, ligaments, and tendons, as well as be due to a reduced functional use of joints resulting from a lack of muscular stabilization and/or muscular imbalance in tetraplegic patients [24–27]. It can also present as fracture-related pain, as pain resulting from heterotopic ossification, or as a consequence of spasticity [28]. The perception of musculoskeletal pain is often restricted to the involved body region and lesioned tissue, respectively. This type of pain can usually be provoked by manipulation of the affected region. A related example would be the tenderness on palpation of a fracture.
2. *Visceral pain* is also a common cause of nociceptive pain in the late chronic phase of SCI and is typically located within the chest (thorax) or in abdominal/pelvic structures, as it is attributed to either disinhibited/increased or inhibited/attenuated activation of the circuitries within the autonomous nervous system [3, 23]. Although evidence-based insights in the underlying mechanisms of abdominal pain are still sparse, recent reports support the already existing notion that constipation is a leading factor [29]. This goes in line with the finding that visceral pain has a late onset, often many years after the SCI [7, 30]. Its clinical presentation is generally diffuse and can be highly unspecific after SCI. While individuals with paraplegia may describe visceral pain as "cramping," "dull pressing," or "causing nausea" similar to nondisabled persons, patients with tetraplegia and visceral pain might in contrast present with complaints that are hardly referable [28]. Thus, symptoms may diminish to nonspecific clinical signs like a general feeling of discomfort/malaise. Important information could be derived from instrument-based or laboratory proof of usual triggers of visceral pain, such as the involvement of the bowels (e.g., constipation/ileus) or the urinary tract (e.g., cystitis) [3], but also a temporal link of pain to increased activity of visceral organs (e.g., postprandial pain) could lead the way to the accurate classification. If there are no clear indications of visceral involvement, another type of pain, such as neuropathic pain, could be present. Here, a permanent presence of pain may support the diagnosis of neuropathic pain.
3. *Other nociceptive pain* is pain that cannot be allocated to the aforementioned subtypes. They may be related or unrelated to SCI, but should fulfill the criteria of nociceptive pain [23]. Those, for instance, include pain due to pressure ulcer or headache as a consequence of autonomic dysreflexia.

12.4 Neuropathic Pain

Neuropathic pain represents a significant socioeconomic burden – both at individual and societal levels, as it is associated with high levels of morbidity and large direct and indirect costs [9, 31]. Neuropathic pain is not a term applied to a single underlying mechanism or disease, but describes a syndrome of various sensory symptoms and signs (e.g., spontaneous ongoing pain, allodynia, and painful attacks). Allodynia is pain due to a stimulus that does normally not provoke pain (e.g., pain evoked by light touch or cold) [32]. Hyperalgesia, which is an increased response to a stimulus that is normally painful [32], may also be present on examination and is differentiated according to the test stimulus (e.g., cold, warm, punctuate, or static mechanical). In general, neuropathic pain is defined as pain caused by a lesion or disease of the somatosensory nervous system [33]. It is divided into peripheral and central neuropathic pain depending on whether the lesion or disease is in the peripheral (nerve root or nerve) or central (brain or spinal cord) nervous system.

Following SCI, patients may experience central neuropathic pain due to the spinal cord lesion or peripheral neuropathic pain due to a lesion or compression of the nerve roots, including cauda equina. Because of the difficulty in distinguishing between peripheral and central pain in some cases, neuropathic pain following SCI is classified into *at-level* and *below-level* neuropathic pain [23]. Patients with SCI may have *other* neuropathic pain, which is pain that is not caused by the SCI but instead by, e.g., thoracotomy due to intercostal nerve injury or carpal tunnel syndrome due to wheelchair use. Other neuropathic pain can be located at, above, or below injury level.

12.4.1 Clinical Characteristics of Neuropathic Pain

At-level neuropathic pain is located anywhere within the dermatome of the neurological level of injury and/or three dermatomes below this level [23]. Pain caused by damage to the cauda equina is always classified as at-level pain, also in cases where it extends more than three dermatomes below the neurological level. *Below-level* neuropathic pain is located in the region more than three dermatomes below the neurological level of injury, but may extend to the at-level area. Neuropathic pain is often described as shooting, pricking, squeezing, or burning. Allodynia – most often to touch or cold stimuli and hyperalgesia to pinprick or thermal stimuli – may be present.

Neuropathic pain following SCI may occur immediately at the time of injury but may also have a delayed onset up to several months. At-level neuropathic pain often has an earlier onset than below-level pain [7]. Neuropathic pain may diminish or resolve during the first year [34], but often becomes chronic, and patients who experience neuropathic pain at 6 months are likely to have neuropathic pain with the same intensity 5 years after their SCI [7]. Paresthesia, which is described as abnormal sensations that are not painful or unpleasant, and dysesthesia, which is described

as unpleasant abnormal sensations, are often present following SCI, e.g., an ongoing tight sensation or a tingling sensation occurring either spontaneously or evoked by, e.g., touching the area.

Recent studies have found that early sensory hypersensitivity predicts later development of central pain [8, 35]. In one study in incomplete SCI, sensory hypersensitivity (mechanical allodynia and temporal summation of pain) and hyperpathia in the first months after SCI preceded ongoing below-level SCI pain [35], whereas in another study, early (1 month) sensory hypersensitivity (particularly cold-evoked dysesthesia) was a predictor of the development of below-level SCI pain [8]. Interestingly, sensory hypersensitivity did not predict at-level SCI pain, supporting that these two pain types are two different pain phenomena, presumably with different underlying mechanisms [7].

12.4.2 Mechanisms of SCI Neuropathic Pain

The mechanisms involved in SCI neuropathic pain are multiple and only incompletely understood. A SCI allegedly causes irreversible functional changes in the vicinity of the lesion site. These include neuronal hyperexcitability, impaired modulation from interrupted supraspinal control, and destroyed spinal circuitries. Insights from animal models indicate the presence of regenerative processes that are characterized by structural adaptions (e.g., rewiring of axonal connections) and changes in signal transmission on cellular level [36–39]. Besides its assumed linkage to spontaneous recovery after SCI, this so-called plasticity may also cause fundamental changes in the transmission of pain signals and therefore lead to detrimental effects with neuropathic pain as a possible consequence. Such neuronal changes include an increased sensitivity to sensory stimuli and a disturbed balance between excitation and inhibition. Ongoing spontaneous activity in central pain pathways rostral to the site of injury are thought to cause spontaneous pain, and neuronal hyperexcitability may cause increased pain to painful stimuli, decreased pain thresholds, aftersensations, and spread of pain. Central sensitization is defined as increased responsiveness of nociceptive neurons in the central nervous system to normal or subthreshold afferent input [32]. Several molecular changes seem to be involved, including changes in the N-methyl-D-aspartate (NMDA) and other glutamate receptors [40], sodium, calcium, and potassium channel expression [41, 42], glia cell activation and release of pro-inflammatory cytokines [41, 43–45], degeneration of inhibitory dorsal horn interneurons containing γ-aminobutyric acid (GABA) [46], and loss of inhibition from descending pathways, dependent on monoamines such as noradrenaline, serotonin (5-HT), and dopamine. Significant structural changes lead to reorganization, such as intraspinal sprouting of calcitonin gene-related peptides and substance P containing fine primary afferents and Rac1-regulated remodeling of dendritic spines on dorsal horn neurons [47–50].

There is evidence from human studies to support that the changes occurring at the injury site of the spinal cord are important for both at- and below-level pain. In some cases, spinal transection and dorsal root entry zone (DREZ) lesions may relieve both at- and below-level pain, suggesting that the area around the spinal lesion acts as a

pain generator. However, these procedures also carry the risk of development of central pain [51–53]. It has also been shown that sensory hypersensitivity at the level of injury and that the percentage of rostral gray matter lesions are highest in patients with below-level pain [54, 55]. It is hypothesized that ectopic activity arising at the rostral part, transmitted via multisynaptic propriospinal pathways, may also play a role in SCI pain [54]. Activity in residual spinothalamic tract neurons may additionally contribute to the generation of pain after SCI [56]. In addition to changes in neuronal excitability at the spinal cord level, changes can be demonstrated in different brain areas following SCI, e.g., the thalamus [57, 58], anterior cingulate cortex, right dorsolateral prefrontal cortex [59], and the somatosensory S1 cortex [60]. Furthermore, pain may be associated with a specific electroencephalography (EEG) signature with increased power in the theta and alpha bands in the relaxed state [61]. The specific role of these changes in generation or modulation of pain is unknown. In summary, neuronal hyperexcitability at the level of injury, spared polysynaptic pathways, and partially spared spinothalamic tract neurons, together with deafferentation resulting in abnormal neuronal brain activity, are possible mechanisms that are involved in the development and manifestation of SCI neuropathic pain.

Experimental models are crucial for improving our understanding of molecular SCI pain mechanisms and for testing new drugs. Assessing pain-like behavior in animals is, however, challenging [62], particularly after central nervous system lesions [63, 64]. Due to the development of the spastic syndrome, the specific assessment of pain-like behavior in rats with SCI cannot rely on the evaluation of simple reflexes and withdrawal thresholds but requires tests that involve brainstem-dependent responses such as licking, guarding, and escape or more complex, cerebrally mediated behaviors.

12.5 Diagnosis of Pain and Its Clinical Distinction

Considering its different manifestations and bearing in mind the potential overlapping of their symptoms, diagnostics of pain related to SCI are challenging [17–19]. Substantial impairment of sensory function below the level of lesion renders the interpretation of symptoms even more difficult.

Assessing the medical history of patients with pain should comprise an exact evaluation of all aspects of the symptoms including the course, impact, and multidimensional aspects of pain. The distribution of pain should be mapped on body charts. The pain intensity can be assessed using a categorical scale, such as mild, moderate, or severe. Other one-dimensional scales are often used, e.g., an 11-point numeric rating scale (NRS) from 0 to 10, where 0 indicates “no pain” and 10 “worst possible pain” or “most intense pain imaginable.” Average and worst pain is often assessed. Since not all sensory symptoms that could occur in neuropathic pain are constantly rated as pain (e.g., tingling), it may be useful also to assess unpleasantness. The character and quality of pain, its onset and time course, aggravating and alleviating factors, and associated symptoms should be included in the evaluation. The impact of pain on daily life refers to its impact on quality of life, function,

sleep, mood, and social relations. The International Spinal Cord Injury Core Data Set has been developed to assist physicians in collecting relevant data related to pain in a standardized way. The dataset includes classification, location, temporal aspects, intensity, impact, and treatment of pain [65].

Reliable and valid differentiation and classification of pain types are needed. Positive diagnostic criteria and a grading system of definite, probable, and possible presence of neuropathic pain have been published [66]. Four criteria need to be fulfilled for the definite presence of neuropathic pain: (1) a history of a relevant nervous system lesion, (2) at least one test confirming such a lesion, (3) pain located in an area of the body consistent with the location of the lesion, and (4) negative (e.g., hypoaesthesia) and/or positive (e.g., allodynia) sensory perception in the painful area. If the pain is not a primary consequence of movement, inflammation, or other local tissue damages and if it is described as burning, shooting, squeezing, painful cold, or electric shock-like or is associated with allodynia, it is likely to classify the pain as neuropathic pain [23]. Nevertheless, a careful examination to exclude other causes of pain is obligatory, and the correct classification of pain into neuropathic and nociceptive pain may still be challenging.

The neurological examination is essential for the diagnosis of neuropathic pain. The International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) serves as a reliable and valid basis for clinical examination of sensory and motor function [67], but it is recommended to perform additional sensory examinations including sensory thresholds to touch, vibration, pinprick, and thermal stimuli. Dynamic mechanical allodynia can be assessed by brushing the skin lightly using a small brush or cotton wool. Aftersensations, i.e., pain continuing after the stimulation has ceased, may be observed. More sophisticated assessments such as quantitative sensory testing (QST); electrophysiological examination using, e.g., laser evoked or contact heat evoked potentials (LEPs and CHEPS); and imaging (e.g., X-ray, CT, MRI) may provide additional insights [68].

Simple questionnaires have been developed for identifying patients with neuropathic pain. The Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) scale [69], the Neuropathic Pain Questionnaire (NPQ) [70], the 10-item questionnaire DN4 [71], IDPain [72], painDETECT [73], and the Pain Quality Assessment Scale (PQAS) [74] are simple patient-based screening questionnaires partially with a short sensory examination that may help to detect the presence of neuropathic pain [75]. Recently, a spinal cord injury pain instrument (SCIPI) has been developed [76]. In most of the questionnaires, pricking pain, electric shocks, burning, numbness, and increased pain to touch are defined as indicators for neuropathic pain. These screening tools seem to have lower psychometric properties when applied to SCI patients than to the general population [77].

12.6 Psychological Aspects of Pain

Psychosocial factors may influence the patients' pain perception and subjective grading of pain. For example, affective disorders, level of independence from caregivers, level of social support, and a lack of efficient coping strategies are of

relevance in this respect and are reported to be associated with greater severity of pain [78–80]. These factors may cause a deterioration of pain or may result in greater psychological distress. It is therefore important to evaluate psychological functioning and the impact of pain on its clinical development. There is also existing evidence for effective psychotherapeutic therapy approaches in complementary treatment and coping of pain, respectively. Such strategies comprise self-hypnosis and biofeedback relaxation training, as well as cognitive behavioral therapy, generally embedded in a multimodal therapy approach [81–84].

12.7 Therapy

Treatment approaches in SCI-related pain range from physiotherapeutic measures through unspecific and specific pharmacotherapy to instrument-based approaches, all with significantly varying levels of evidence for the given indication. The diagnosis of pain type is the first important step. If possible, the underlying cause of pain should be treated, and when this is not possible, symptomatic treatment of the pain and the related disability should be offered. Realistic expectations about the outcome of a given treatment should be discussed with the patient. During the course of pain treatment, the level and character of the pain and side effects should be carefully monitored. When the pain has become chronic and is associated with disability, a multidisciplinary approach is preferred, and it is important to evaluate and treat any associated depression, sleep disturbance, and psychological distress. Disciplines, for instance, could comprise psychologists, physiotherapists, neurologists, and orthopedists/trauma surgeons and, if necessary, specialized pain therapists.

12.7.1 Treatment of Nociceptive Pain

Nociceptive pain is considered to be amenable to certain therapeutic strategies, including interventional but also nonsurgical and instrument-based therapies. The level of evidence for these approaches is varying to a large degree and sometimes it is very low.

Whenever possible, therapy should primarily focus on the elimination of the underlying causes, such as administration of laxatives, fracture treatment, wound care, or reduced stress on overused joints [85]. Surgical interventions addressing arthrosis or ankylosis of the shoulder joint in patients with paraplegia are subject to controversial discussions. Even though reported to be effective following a careful risk-benefit analysis and in consideration of the time and costs for the post-interventional rehabilitation period, such complex interventions should only be considered with caution in SCI patients due to a high risk for recurrent articular complaints [86–89].

The second mainstay of routinely applied therapy strategies is represented by mostly temporary pharmacological treatment. This approach includes nonsteroidal anti-inflammatory drugs (NSAID), such as ibuprofen or diclofenac, as well as other

non-opioid pain drugs, such as metamizole [85]. In markedly severe cases, opioids could also be an option for symptomatic pain therapy. The "WHO Treatment Guidelines on chronic nonmalignant pain in adults" are currently being developed, but not yet published [90]. Until then, the "WHO's cancer pain ladder for adults" may be used as orientation guideline, since it is a widespread clinical tool that is also commonly used in nociceptive pain management [91, 92]. However, there are still no evidence-based treatment recommendations based on randomized clinical trials in SCI, as well as in general pain therapy of adults. Individualized pain management concepts, based on the underlying pathology, should be considered in given cases [92].

Both aforementioned approaches should always be embedded in a multimodal therapy setting that comprehensively addresses the patient's complaints. Such supportive therapies primarily involve physical therapy, including general or symptom-oriented exercise programs [93–98]. Numerous further non-pharmacological and nonsurgical therapy approaches have already been tested in various studies and/or trials. Among them, acupuncture was found to have beneficial effects on musculoskeletal pain in SCI [99, 100]. However, it does not seem to be superior to the control interventions consisting of physical activity and sham acupuncture, respectively. Instrument-based therapies such as transcranial electrical stimulation (TCES) or transcutaneous electrical nerve stimulation (TENS) have also been tested, especially for their effect on general pain relief, which also includes musculoskeletal pain intensity. Thus, TCES and TENS admittedly delivered indications for efficacy in this context, yet existing clinical trials are few, methodically heterogeneous or not focused on SCI pain [101–108]. Furthermore, low or insufficient evidence of efficacy in SCI-related musculoskeletal pain has yet to be stated for conservative methods, such as massage, heat therapy, or behavioral management (e.g., hypnosis or cognitive behavioral therapy) [81, 109–112]. In consequence, if and to what extent such a therapeutical regimen should be added has to be decided on an individual basis.

12.7.2 Treatment of Neuropathic Pain

If possible, the underlying causes should be treated, but often symptomatic treatment is the only option. So far, no treatment has proven successful in preventing neuropathic SCI pain. It is important to exclude other causes of pain such as musculoskeletal pain and to consider factors that may aggravate neuropathic pain such as pressure sores, spasticity, or bladder infection. It is also important to evaluate the impact of pain on daily life, sleep and mood, psychological factors, and risk of suicidal ideation.

12.8 Pharmacological Treatment

The Neuropathic Pain Special Interest Group (NeuPSIG) of the International Association for the Study of Pain (IASP) has recently updated the evidence-based treatment recommendations for neuropathic pain [34]. Based on the Grading of

Recommendations Assessment, Development, and Evaluation (GRADE) system, pregabalin, gabapentin, serotonin-noradrenaline reuptake inhibitors (SNRIs), and tricyclic antidepressants (TCAs) have strong recommendations for use in neuropathic pain. Opioids and a combination of selected first-line agents have weak recommendations, whereas there are weak recommendations against the use of cannabinoids and valproate and strong recommendations against the use of levetiracetam and mexiletine. No studies have examined the efficacy of nonsteroidal anti-inflammatory drugs (NSAID) and paracetamol in neuropathic pain. Certain topical agents are also recommended for peripheral neuropathic pain. Thus, NeuPSIG recommends pregabalin, gabapentin, SNRIs, and TCAs as first-line drugs, tramadol as second-line, and other opioids as third-line treatments for central neuropathic pain [34]. Data for other drugs such as NMDA antagonists and other anticonvulsants were inconclusive. However, a trial of such drugs, e.g., oxcarbazepine or lamotrigine, may be indicated in certain conditions and by pain specialists.

Randomized controlled trials (RCT) in SCI neuropathic pain support these recommendations (Table 12.2). Patients with SCI may, however, be particularly vulnerable to CNS-related side effects, including dizziness and somnolence, which may be due to their frequent use of spasmolytic drugs [113, 114]. It is also important to be aware that pain relief is moderate and only effective in a subgroup of patients.

Table 12.2 Summary of randomized double-blind, placebo-controlled trials with at least ten patients and with a treatment of at least 3 weeks

Study	Drug, final daily dose, number randomized	Outcome	NNT
Antidepressants			
[129]	Amitriptyline 150 mg, 38	p	ns
[130][a]	Duloxetine 60, 120 mg,	n	
Anticonvulsants			
[113]	Pregabalin 600 mg, 137	p	7.0 (3.9–37)
[131][a]	Pregabalin 600 mg, 40	p	3.3 (1.9–14)
[115]	Pregabalin 600 mg, 220	p	7.0 (3.9–31)
[132]	Gabapentin 3600 mg, 20	p	NA
[129]	Gabapentin 3600 mg, 38	n	
[133]	Levetiracetam 3000 mg, 36	n	
[134]	Valproate 2400 mg, 20	n	
[135]	Lamotrigine 400 mg, 30	n	
Miscellaneous			
[114]	Tramadol 400 mg, 36	p	ns
NCT01606202[b]	Sativex spray, 111	n	
[136]	Mexiletine 450 mg, 11	n	

NNT numbers needed to treat to obtain one patient with a 50 % pain reduction, *CPSP* central poststroke pain, *SCI* spinal cord injury, *p* positive, *n* negative, *NA* dichotomous data not available, *ns* no significant difference in numbers of patients with 50 % pain reduction during active and placebo treatment

[a]Included both SCI pain and central poststroke pain

[b]Data from clinicaltrials.gov

Pregabalin and gabapentin, including gabapentin extended release and enacarbil, are structurally related compounds. Their analgesic effect in neuropathic pain is thought to be mediated through antagonism of the $\alpha_2\delta$ subunit of voltage-dependent calcium channels at presynaptic sites. The most common side effects are somnolence and dizziness, which seem particularly bothersome in SCI [113, 115]. Other side effects include peripheral edema, nausea, and weight gain. Gabapentin is administered three times daily with slowly increasing dosage, e.g., starting with 300 mg the first day and increased by 300 mg every 1–7 days. The final daily dose is between 1800 and 3600 mg. Pregabalin is administered twice daily and slowly titrated from 75 or 150 mg daily to 600 mg daily. In SCI individuals with renal impairments, lower doses are used.

Antidepressants have a comparatively weaker body of evidence with regard to RCT but are also used in neuropathic pain treatment. These include TCAs (e.g., amitriptyline, imipramine, and nortriptyline) and SNRIs (duloxetine and venlafaxine), whereas the effect of selective serotonin reuptake inhibitors (SSRIs) is even less certain [34]. Antidepressants block the reuptake of noradrenaline and serotonin, and TCAs also have other actions such as a blockade of sodium channels. Side effects to TCAs include dry mouth, somnolence, constipation, urinary retention, orthostatic hypotension, and sweating. TCAs are contraindicated in patients with epilepsy, heart failure, and cardiac conduction blocks, and an electrocardiogram (ECG) is needed before initiating treatment. There is a large pharmacokinetic variability in the metabolic pathways of TCAs, and the final dose varies considerably among patients. TCAs should be slowly titrated stating with 10 or 25 mg daily up to 50–150 mg daily. Side effects to SNRIs include nausea, somnolence, dizziness, constipation, and sexual dysfunction. Duloxetine can be initiated with 30 mg and increased to 60 mg daily, while venlafaxine can be started at 37.5 mg and increased slowly up to 150–225 mg daily. If treatment with a single drug is only partly effective, combination therapy can be tried. Side effects, e.g., somnolence and dizziness, need to be carefully monitored, and it is important to be aware of specific side effects, e.g., the serotonin syndrome, which, for example, can occur when combining SNRIs such as antidepressants and tramadol. It is characterized by flu-like symptoms, rapid heart rate, high blood pressure, nausea/vomiting, and heavy sweating and can lead to agitation, confusion, hallucination, and muscle rigidity. High fever, irregular heartbeat, seizures, and unconsciousness are eventually symptoms in severe cases of the serotonin syndrome.

In severe refractory neuropathic SCI pain, intrathecal treatment with clonidine and morphine [116] or with ziconotide or morphine, either alone or added to baclofen treatment, may be considered, but there is limited knowledge about long-term efficacy and safety, and usually the effect is unpredictable with only a small percentage of patients responding [117, 118].

12.9 Non-pharmacological Treatment

Neurostimulation techniques such as transcranial direct current stimulation and repetitive transcranial magnetic stimulation or invasive procedures such as motor cortex stimulation and spinal cord stimulation are being tested, but results are

conflicting with very few data on long-term efficacy and safety [119–125]. In a recent study, the combination of transcranial direct current stimulation and visual illusion reduced SCI pain, but the treatments given alone had no or limited effect [126]. Dorsal root entry zone (DREZ) is not recommended [125].

Cognitive behavioral programs have been shown in RCTs to improve the sense of coherence and depression [83] and to reduce anxiety and increase participation in activities [127], although no effect on pain intensity was seen. An exploratory study also found an effect on pain intensity and pain-related disability of a multidisciplinary cognitive behavioral program for coping with neuropathic SCI pain [128]. Such programs as well as other psychological treatments, e.g., hypnosis [84], may thus be valuable additions to the treatment.

Summarizing, although certain non-pharmacological treatment approaches in SCI-related chronic neuropathic pain are believed to be beneficial, a convincing basis of evidence is still lacking [108].

Conclusion

Pain is a common and relevant complication in SCI. Its assessment and therapy can be major challenges. Musculoskeletal pain is common in the acute phase, and musculoskeletal, neuropathic, and visceral pain are the most common types of pain in the chronic phase.

Assessment of pain in SCI, including its characterization and assignment to specific pain types (nociceptive vs. neuropathic), is still being optimized with respect to reliability and validity. While most of the currently established questionnaires have not been developed to specifically assess pain in SCI, recent publications increasingly focus on the verification of appropriate SCI-specific assessments to account for particularities in manifestation of different SCI pain types.

Pain can have a severe impact on the patients' rehabilitation, sleep, mood, and quality of life. A multidisciplinary approach to treatment on an individual basis is thus needed. A better understanding of the underlying mechanisms is needed to develop more promising therapy strategies and to be able to prevent the development of chronic pain. Yet, in all aforementioned SCI-related pain types, clinically established therapy approaches comprise non-pharmacological and/or pharmacological treatments. While interventional and pharmacological therapies of nociceptive and visceral pain are mainly aiming for identification of causalities and their resolution, therapeutic approaches for neuropathic pain are largely focused on an assumed modulation of neuronal hyperexcitability and decreased inhibition. A lot of these options are mainly applied on empirical basis, like the application of laxatives in neurogenic bowel dysfunction to relieve visceral pain. Others, like the administration of antidepressants in SCI-related neuropathic pain, are based on partially scarce evidence. Given this fact, therapeutic decisions should admittedly be made in accordance with current guidelines or, if not applicable, at least be based on publications of national or international associations/societies, which are representing the field of SCI.

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Spasticity

13

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Abstract

As has been said of certain forms of art, spasticity is difficult to define, but "You know it when you see it." After upper motoneuron damage due to spinal cord injury, spinal circuitry receives unbalanced input from peripheral afferent fibers and segmental interneuronal circuits relative to descending supraspinal pathways. This results in a mostly detrimental clinical syndrome of distorted motor control that contributes as much as frank weakness does to hindering execution of activities of daily living.

In this chapter, we elaborate on our current understanding of the physiological mechanisms underlying post-SCI spasticity in humans, its evolution, its assessment, and a spectrum of clinical interventions. We end by discussing future directions of investigation that could position clinicians to help patients reestablish volitional control over the altered circuitry that underlies spasticity.

13.1 Introduction

To put it simply, spasticity is more complex than we would like. Spasticity encompasses a broad range of abnormal motor behavior that results from upper motoneuron damage. This causes increased muscle tone, increased muscle reactivity, decreased precision of voluntary muscle control, and the emergence of involuntary motor output. All of these effects may show differences over time, under static versus dynamic conditions, flexor versus extensor movements, and numerous other permutations. Though some aspects of spasticity may prove useful to assist in weight bearing, more often stiffness, pain, and uncontrollable spasms significantly interfere with activities of daily living and quality of life [1–3].

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Classical teaching dictates that increasing severity of SCI correlates with decreased volitional movement and increased spasticity. However, spasticity severity does *not* in fact linearly correlate with injury severity [2]. On the contrary, spasticity tends to be more severe after moderate injury, whereas mild or very severe SCI demonstrates fewer clinical features. Thus, spasticity circuitry and dynamics are far more complicated than they appear. The only way to successfully treat spasticity, and to exploit its underlying potential, is to better understand it.

13.2 Evolution from Shock to Spasticity

Spasticity takes time to develop. Immediately after injury, spinal motoneurons may go into a period of shock clinically manifested by total paralysis, flaccid tone, and unobtainable deep tendon reflexes caudal to the injury level [4]. Polysynaptic cutaneous reflexes such as the bulbocavernosus and the cremasteric reflexes may persist during the period of shock except in the most severe cases [5, 6].

Electrophysiologically, alpha motoneurons demonstrate hyperpolarization and reduced excitability (loss of F-wave responses (see chapter 11)), likely reflecting inactivation of persistent inward currents and loss of excitatory supraspinal input, especially from descending adrenergic and serotonergic pathways [4, 5, 7, 8]. H-reflexes (see chapter 11), the electrophysiological equivalent of the monosynaptic tendon stretch response, begin to return within 24–72 h, usually before deep tendon reflexes become clinically detectable [4, 7, 8]. This discrepancy sheds light on the role played by the muscle spindle end organ: during spinal shock, hypoexcitable gamma motoneurons lead to decreased spindle resting tone [7, 8]. These hypoactive spindles become less responsive to tendon stretch [9]. The electrically triggered H-reflex elicits greater responses than clinically triggered stretch reflexes via two mechanisms: one, the H-reflex bypasses muscle spindles to directly activate Ia afferents, and two, the H-reflex results in a more synchronous afferent volley that may lead to greater excitatory postsynaptic potentials (EPSP) summation at the motoneuron [5, 8, 9]. Likewise, the early presence of cutaneous reflexes such as the bulbocavernosus and cremasteric responses, which are cutaneous reflexes that do not depend on muscle spindles, further implicates spindle and gamma-motoneuron suppression as key mechanisms of deep tendon areflexia during spinal shock.

As spinal shock begins to resolve, the traditional dogma of reflexes returning in a caudal-to-rostral direction is not borne out by the data [5, 6]. Polysynaptic cutaneous reflexes such as the delayed plantar response (S1–S2) and the cremasteric (L2) may be present prior to that of the bulbocavernosus (S2–S5) [4, 6]. Patellar tendon stretch reflexes may return prior to Achilles tendon reflexes [5]. Electrophysiologically, this transition phase is marked by the return of persistent inward currents and F-wave responses, manifesting in increased alpha-motoneuron excitability [5, 7]. Once reflexes return, they are almost immediately larger than prior to injury, which may be due to a combination of loss of descending inhibitory influences and afferent plasticity such as sprouting [4, 10].

There is no sharp demarcation between the phase of regaining reflex activity (days to weeks) and the acquisition of the spastic state (weeks to months). Overcompensation represents one factor leading to spastic hyperactivity – as part of the adaptations that occur in response to altered signaling across the lesion, neural segments below the injury increase neurotransmitter receptor expression and constitutive activity [4, 7, 10, 11]. Additionally, structural plasticity involving axonal sprouting and dendritic spine restructuring leads to new synapse formation [10, 12]. However, faulty inhibitory regulation of these newly forged connections allows spreading of the hyperreflexic state along multiple axes, such as rostro-caudally (S1 sensation now activating L5 motoneurons in the Babinski reflex) or across the midline (crossed adductor reflexes). Furthermore, pathological reflexes begin to emerge, such as the Hoffman and Babinski. Extensor and flexor spasms, often involving multiple body regions, are elicited spontaneously or by otherwise benign stimuli. Prolonged muscle spasms also derive from re-expression of persistent inward currents combined with reduced inhibition of motoneuron excitatory postsynaptic potentials in response to brief sensory stimuli [7, 13]. Stiffening of nonneuronal tissues such as muscle and tendon further exacerbates increases in passive limb tone [7, 14]. The combination of hyperexcitable alpha and gamma motoneurons, reduction in segmental interneuronal inhibition, and altered muscle and tendon composition all contribute to chronic spasticity.

It finally should be pointed out that the profile of hyperreflexia, hypertonia, spasms, and even dyssynergias found in any patient is context dependent, varying with pain, position, movement (passive or attempted), fatigue, or state of arousal. There are also differences between patients that are difficult to explain or quantify, but well known to many clinicians: among two patients with otherwise similar injuries, one may be relatively flaccid at rest but stiffen with movement, whereas the other may be stiff at rest but regains fluidity with the initiation of movement.

13.2.1 Clinical Impact

Spasticity is not universal after SCI. Its prevalence varies according to injury level, injury severity, injury pattern, time since injury, and a range of other factors. For example, an individual with mild upper cervical central cord injury may have worse spasticity in the arms than the legs, whereas an individual with the same central cord injury slightly more caudally may have decreased tone in the arms relative to the legs. A person with diabetes and SCI may have pathologically brisk patellar tendon reflexes but absent reflexes at the ankles due to overlying peripheral neuropathy. In many cases, the relationships between these factors are neither linear nor intuitive – two people with injuries that appear identical may have drastically differing spasticity symptoms; a person with relatively mild SCI may suffer from worse spasticity than a person with severe SCI. These inconsistencies belie the fact that spasticity pathophysiology is complicated. Therefore, better understanding this physiology could lead to new and better treatments. Below we will summarize basic spasticity epidemiology and clinical relevance.

Spasticity has a rostral-to-caudal prevalence gradient. Among a group of individuals with chronic SCI, those with cervical injuries were the most likely to report symptoms of spasticity (79 %), followed by thoracic (69 %) and lumbosacral (22 %) [2]. The low degree of spasticity in lumbosacral SCI is unsurprising, as these injuries are more likely to damage lower motoneurons and emerging nerve roots rather than descending supraspinal circuits. As hinted above, the effect of injury severity is not straightforward – in the Sköld study, individuals with cervical injury were more likely to have spasticity in cases of complete (93 %) rather than incomplete (78 %) sensorimotor loss, whereas those with thoracic injuries were equally likely (72 % complete, 73 % incomplete) [2]. It may, however, be of limited use to characterize spasticity in terms of clinical "completeness" as up to two-thirds of clinically "complete" patients can be shown to be neurophysiologically "discomplete," with evidence of residual supraspinal influence over infra-injury segmental neural circuitry [15, 16].

Because of its predilection for extensor muscle tone in the legs, spasticity may provide beneficial effects on weight bearing and the ability to make transfers [1, 7]. In theory, spastic muscle activity should reduce the rate of osteoporosis in large leg bones that occurs after SCI. However, the evidence for this is sparse and conflicting [17–20]. As a component of the upper motoneuron syndrome, it is more clear that spasticity maintains muscle mass to some degree, at least more so than in cases of severe SCI with flaccid paralysis, or in cases with lower motoneuron damage.

Although spasticity is only rarely considered beneficial, that does not mean that it should automatically be judged as detrimental. Furthermore, treating the "positive" post-SCI symptoms of spasticity often worsen the "negative" post-SCI features of weakness [11]. Therefore, treating the patient should take precedence over treating the examiner. Less than half of individuals with chronic SCI and spasticity considered their symptoms problematic [2, 21–23]. Problematic symptoms include painful large muscle spasms, co-contracting agonist-antagonist muscles that interfere with effective movements, and stiffness that hinders comfortable positioning in a chair or bed. Detrusor sphincter dyssynergia (DSD) represents a special case of spastic co-contraction, as the external urethral sphincter inappropriately contracts while the detrusor muscle attempts to squeeze urine out of a full bladder. DSD is a major cause of urinary tract infection and renal impairment [24]. All of these symptoms conspire against performing activities of daily living such as sleeping, dressing, bathing, and mobility.

Thus, spasticity's effect on daily living may range from inconsequential to helpful to significantly disabling. Often, all of these effects coexist within an individual, again, depending on the time and circumstance. Triggers such as specific movements, medications (including antidepressants), time of day, weather patterns, infection, and others can exacerbate spasticity symptoms [25–27]. Left untreated or undertreated over the long term, shortened muscle fibers become more difficult to stretch, accompanied by connective tissue changes in the associated tendons and joints, resulting in contractures or fixed immobility of muscles and joints that can only be partially treated surgically [7, 14]. As will be discussed later in this chapter, the ideal treatments for spasticity should *enhance* patterned nervous system activity,

not throw a nonspecific inhibitory blanket over it. Individualized approaches that incorporate multiple non-pharmacological treatment modalities will maximize the likelihood of improving both positive and negative symptoms after SCI.

13.2.2 Physiological Considerations

It is tempting to oversimplify the spastic state: disconnection from supraspinal control leads to excessive reactivity of motor circuits below the injury. This oversimplification ignores multiple levels of complexity – the fact that most spinal injuries spare a varying proportion of supraspinal inputs (and their ascending sensory feedback); the dynamic balance of excitation and inhibition among spared supraspinal inputs; plasticity in sensory afferent and segmental interneuronal projections and synaptic connections; and finally the reconfigured balance between residual descending input, sensory input, segmental interneuronal circuits, and motoneurons. All of these factors, and likely other unknowns, prevent a simplistic explanation or model for predicting spasticity after SCI. It is likewise difficult to determine the interaction of spasticity and neurological recovery; spasms or the emergence of other spastic features often precede motor recovery after SCI. It is hard to know if both simply represent increased excitability of neural circuitry after injury or whether the changes that give rise to spasticity also give rise to better motor recovery (or vice versa).

Increased passive tone Spastic muscle stiffness derives from neuronal and nonneuronal factors. Neuronally, increased resistance to passive movement stems from hyperactive muscle stretch reflexes [28, 29]. As noted earlier, hyperreflexia results from multiple factors, including hyperactive spindle afferents, reduced presynaptic inhibition of those afferents, constitutively depolarized motoneurons, and reduced descending facilitation of segmental inhibitory circuits [4, 7, 30–33]. Additionally, "normal" sensory stimuli may induce pathologically prolonged motoneuron responses, partially due to prolonged motoneuron inward currents and to hypersensitivity of N-methyl-D-aspartate (NMDA) transmission in excitatory segmental interneurons [7, 33].

The classic clinical definition of "velocity-dependent" hypertonia simply reflects that faster passive muscle stretch results in a stronger antagonistic contraction due to greater and more synchronous activation of Ia afferents. Whether this is simply an exaggerated version of the normal response to muscle stretch or a qualitative shift in the slope of the velocity-dependent curve is debated [34]. The clinical "clasp-knife" phenomenon describes a joint that is stiffer at the beginning of its passive range of motion (ROM), then "gives way" over the remainder of the range of motion. The clasp-knife phenomenon has been harder to explain physiologically but is likely due to an exaggerated withdrawal reflex and the excitation-decay patterns of segmental interneurons [35, 36].

Nonneuronal changes further exacerbate passive hypertonia – muscles and tendons atrophy and undergo fibrosis and other biomechanical transformations [14, 28,

37]. Aside from directly causing muscle stiffening, these alterations in connective tissue composition more efficiently transmit muscle stretch to the spindles, leading to yet greater stretch reflex responsiveness [34].

Increased active tone In individuals with residual spared spinal circuitry, spasticity may worsen dramatically with active volitional movement – an attempt to walk causes a painful whole-leg spasm and fall; an attempt to eat causes sudden elbow flexion and a too-close encounter with a fork. These are examples of dyssynergias between agonist and antagonist muscles that hinder performance of fractionated fine motor functions. This stems from reduced function of segmental reciprocal inhibitory interneurons [32, 38] and poor signal targeting due to incompletely damaged supraspinal tracts and their sprouts, and the act of volitional muscle contraction itself can exacerbate stretch responses [34].

The duality of supraspinal influence Inconveniently, spasticity does not perfectly correlate with SCI severity. This speaks to the multifaceted role played by supraspinal pathways in facilitating and inhibiting movement, both directly and via segmental interneuronal circuits. Even individual descending tracts exert seemingly contradictory influences on muscle tone depending on ongoing limb positions and phases of movement – in other words, intraspinal circuitry processes the same supraspinal signals differently depending on intraspinal and peripheral states of movement [38–40]. This complexity results partially from the fact that many descending supraspinal pathways terminate in overlapping synaptic target zones that include interneurons with both facilitatory and inhibitory roles on flexor and extensor motoneuron pools. In effect, in both human and other animals, the spinal cord makes the real decisions on how to execute movements by filtering, processing, and integrating this multimodal input from supraspinal and peripheral sources [11, 41–43].

Some insight has been gained into the complexity of supraspinal influence using animal models with specific types of lesions [30]. Most rodent models of SCI, however, do not result in a spasticity syndrome that resembles the human clinical state, at least not in terms of a relationship between the severity of injury and the observed "phenotype" of spasticity. Investigators who study both human and animal SCI can identify that humans with clinically and neurophysiologically complete SCI rarely show any spasms, but rats with complete transections demonstrate high-amplitude, rapid/ballistic movements not unlike spasms in humans with incomplete SCI. Rats with incomplete SCI from experimental spinal cord contusions often show abnormal movements that would be more likely described as dystonic or athetoid. This has been speculated to indicate that animal movement is more intrinsic to the cord, whereas human movement relies more strongly on supraspinal direction [30]. It may be more accurate to describe spasticity as resulting from interruption of *descending* fibers, whether their origin is cortical, bulbar, or spinal. For example, rat cord transection at S2 caused tail hyperreflexia, cutaneous hypersensitivity, clonus, and increased H-reflex amplitude. The authors of that work speculated that the

observed spasticity after S2 lesion reflected that rat tail movement depends upon descending propriospinal fibers from the lumbar region, analogous to human limb movement depending upon descending supraspinal fibers [30].

13.2.3 Assessing Spasticity

A myriad of tools and scales have been used to assess spasticity in both the clinic and research realms. Due to spasticity's complexity, variability, and dynamic nature, as well as the subjective nature of many of its assessments, none have proven optimal. The need remains for the development of consensus tools to objectively quantify different domains of the spastic state. The National Institute of Neurological Disorders and Stroke (NINDS) Common Data Elements (NINDS CDE) initiative (https://commondataelements.ninds.nih.gov/SCI.aspx) has defined the modified Ashworth Scale (mAS) as one evidence-backed assessment tool that could be used as a supplementary outcome in clinical studies. However, effective interpretation and integration of this information into the overall clinical picture will require incorporating more objectivity and more "metadata" into each assessment – a standardized format for recording which joints are assessed, time of day, timing in relation to patient's recent medication intake or physical therapy, the patient's position, the state of relaxation or active movement, and other factors that contribute to assessment variability and unreliability [7, 44] (Table 13.1).

Patient-reported assessments No matter how objective or quantitative the spasticity assessment, its value is lessened if it does not correlate with a patient's own perceptions. The spinal cord injury spasticity evaluation tool (SCI-SET) uses a

Table 13.1 Patient-reported, examiner-graded, and electrophysiological tools for assessing spasticity

Patient-reported symptom assessments
Penn Spasm Frequency Scale
Spinal cord injury spasticity evaluation tool (SCI-SET)
Patient-reported impact of spasticity measure (PRISM)
Clinical assessments of tone
Ashworth and modified Ashworth
Resistance to passive movement (REPAS)
Pendulum test
Tardieu
Clinical assessments of spastic reflexes
Spinal cord assessment tool for spastic reflexes (SCATS)
Deep tendon and cutaneous reflexes (e.g., Babinski, crossed adduction)
Electrophysiological testing
Reflex testing (assessment of hyperreflexia, reflex modulation)
Poly-electromyography (assessment of dyssynergia)

seven-point Likert scale for each of 34 questions to elicit a person with SCI's opinion of the positive or negative impacts made by various elements of spasticity [1]. The Penn Spasm Frequency Scale and patient-reported impact of spasticity measure (PRISM) are other self-assessments relating to how spasticity actually affects an individual's daily life [45, 46]. These types of patient-oriented tools should complement any examiner-based assessment of spasticity.

Ashworth and modified Ashworth Scale (mAS) This is the most widely used assessment in both clinical practice and research settings [47]. While a subject is supine, the examiner subjectively judges the tone of each examined joint through its range of motion, assigning a score on a five- (unmodified) or six-point (modified) scale between 0 and 4:

(0) No increase in muscle tone
(1) Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion when the affected part(s) is moved in flexion or extension
(1+) Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the ROM
(2) More marked increase in muscle tone through most of the ROM, but affected part(s) easily moved
(3) Considerable increase in muscle tone, passive movement difficult
(4) Affected part(s) rigid in flexion or extension

Any joint can be scored, a feature that makes the mAS flexible yet problematic when different joints are assessed by different examiners among different patients on different days. Furthermore, its ordinal scoring range is not linear, and the 1+ score introduces an extra step into quantifying scores across different patients in research studies. Perhaps most importantly, the Ashworth assesses only one component (passive range of motion) of the spastic condition. Thus, despite its universal use, the Ashworth scale's inherent subjectivity, unreliability, and limited scope make its nearly universal use inadequate [44, 48–50]. The Tardieu Scale imposes a longer examination time on both patient and clinician, requires greater clinician expertise, and has similar drawbacks that affect interrater reliability [51]. Some of these issues with subjective clinician assessments were addressed by defining the most informative set of joint evaluations across different subjects using the original five-point unmodified Ashworth scale [52].

Pendulum test This test assesses static tone in the knee joint in a seated subject after release of the leg from an extended position [53, 54]. Though it may be more objective than the mAS, it requires a goniometer for accurate joint angle measurement and use of a rather esoteric formula based on those angles to calculate a spasticity index [55]. These features effectively prevent the pendulum test from any hope of widespread clinical use.

Spinal Cord Assessment Tool for Spasticity (SCATS) This lower extremity assessment in the supine subject gauges polysynaptic reflex responses to provocative maneuvers such as clonus in response to rapid dorsiflexion of the ankle, toe and leg flexor response to a standardized noxious stimulus to the sole of the foot, and leg extensor response to simultaneous extension of the hip and knee [56]. These maneuvers are adapted from traditional neurological examination techniques but scored in standardized fashion. In theory, SCATS encompasses both a more comprehensive (yet still clinically practical) evaluation and a more objective scoring system than the mAS. The delayed plantar response is another pathological clinical reflex that is not technically scored during the SCATS. This involves plantar flexion of the big toe 0.5–1 s after deep noxious plantar stimulation. The presence of the delayed plantar response indicates more severe injury and a worse prognosis [6, 57].

Electrophysiological spasticity assessments The routine use of electrophysiological tools to characterize spasticity in the clinical setting is untenable due to costs associated with equipment requirements, technical expertise needed, and time for testing. As research tools, however, these methods are the most direct assessment of the neurophysiology underlying the altered function of the injured nervous system after SCI. As it developed a formalized list of clinical measures for spasticity after SCI (under neurological outcomes), the NINDS Common Data Elements initiative (https://commondataelements.ninds.nih.gov/SCI.aspx) also developed a list of electrodiagnostic testing procedures to neurophysiologically characterize signal conduction and processing in the injured spinal cord. Some of these address aspects of spasticity.

Poly-electromyography This method studies motor control across *groups* of muscles and is mostly focused on the pattern of muscle activation for standardized voluntary movements or responses to stereotyped sensory input. One such methodology, long studied but only rarely applied, is the Brain Motor Control Assessment (BMCA) [58–62]. The most helpful feature of such an analysis is the quantitative ability to compare the pattern of muscle activity in injury to that for the same motor task in uninjured individuals. In terms of spasticity, such poly-electromyographic analysis can characterize and quantify the extent of dyssynergia seen under specific circumstances. It can also detect the presence of electromyographic activity when there should be none, probably the electrodiagnostic equivalent of resting hypertonia.

Reflex testing Reflex or late responses are an established component of peripheral nerve electrodiagnostic testing, but have not been as commonly used in the context of clinical SCI or in measuring spasticity after SCI. As such, the NINDS CDE electrodiagnostic study group did not find a consensus use of testing reflexes, their conditioning, or their modulation under different circumstances in clinical study application. Nevertheless, SCI researchers regularly study Hoffman (H) reflexes [63], posterior root muscle reflexes (PRMRs) [64], tibial reflexes [65], and others to better understand how SCI changes spinal reflexes to generate hyperreflexia and pathological responses.

13.3 Interventions

The spastic state is not exclusively detrimental. Some individuals may exploit spasticity to improve ambulation or mobility [1]. Therefore, the clinician must not assume the goal of eliminating all signs of spasticity. First and foremost, the clinician must listen to the patient to cooperatively set treatment goals and priorities. One patient may prioritize pain relief and improved sleep; another may insist on optimal mobility and refuse any intervention that could interfere with weight bearing; another may desire to fit into a hand orthotic device [66–68]. As with treating many other medical problems, interventions should be titrated. Begin with the least invasive, non-pharmacological treatments, and then range as necessary toward more systemic and invasive options. It should be noted that most of the non-pharmacological treatments do not show definitive benefit when subjected to systematic review; however, this may indicate the difficulty in standardizing the delivery and dosage of physical interventions in formal clinical rehabilitation trials.

13.3.1 Physical Measures

Passive stretching If a muscle is tight, stretch it. This simple maxim forms the foundation for physical interventions against spasticity. Passive range of motion exercises, either applied by the clinician or ideally self-applied by the affected individual, may reduce hypertonia by directly relieving stiffened intramuscular connective tissue, as well as by inducing accommodation of hyperexcitable muscle spindles and gamma motoneurons [69–72]. The most difficult aspect of passive range of motion exercises is performing them for enough time and repetitions to have a lasting effect. Even "intensive" physical therapy for the typical 2–5 h per week does not make up for the relative muscle inactivity present for the remainder of the 168 h every week. Various types of muscle and joint splints are directed at filling in this inevitable time gap, but when stretching is subjected to systematic review, the overall benefit remains difficult to prove [71–73].

Assisted movements Assisted upright weight bearing, most often using a standing frame, is commonly used both in the clinic and at home in an effort to achieve multiple goals aside from relieving spasticity – orthostatic tolerance to upright posture, relief of pressure from susceptible skin areas, anti-osteoporotic effects of gravity, and subjective benefits to self-esteem. Assisted standing should also simultaneously stretch and strengthen triceps surae muscles and Achilles tendons. Because of these multiple potential benefits and the relative simplicity and safety, standing frames remain a commonly used intervention despite lack of overwhelming evidence [74, 75].

More active assisted movements are intensively studied for potential benefit on motor control, not just spasticity per se. This includes a range of therapist-guided and robotic-assisted options for functional upper and lower extremity movements

(see chapters 22 and 23). For example, body weight-supported treadmill training is directed at lumbar locomotor central pattern generator (CPG) circuits, with the goal of improving CPG coordination and ambulation [76–82]. With more extensive experience in the stroke population, robotic-assisted hand and arm therapy is directed at improving functional reach and grasp motions [83–87]. Both types of therapy may reduce spasticity by replacing aberrant hyperexcitable sensory circuit firing with more functionally appropriate afferent signaling, leading to less muscle spasm and co-contraction [88, 89]. These assisted, pattern-based interventions are thought to induce beneficial neuroplasticity through task-specific learning [41, 90]. It should be noted that to date, the benefits of activity-based therapy have been greater for those individuals with clinically motor incomplete SCI [91, 92]. However, optimism should be retained for those with clinically complete SCI, as combinations of physically assisted therapy with drugs and electromagnetic stimulation may synergize to improve movement in the future even after severe SCI.

Other Physical Measures A variety of other physical measures are used by therapists to deal with hypertonic muscles, spasms, or unwanted movements in response to sensory stimuli. These include heat, ice, vibration, massage, biofeedback, and relaxation techniques. Small studies have used either focal or whole-body vibration at 50–100 Hz in populations of SCI and stroke patients [93–95].

13.3.2 Drugs

Pharmacological approaches to treating spasticity are regularly reviewed [96–98], so instead this chapter will discuss these agents from the perspective of their impact on the broader issue of motor control after SCI. Compared to physical and other non-pharmacological approaches, drug studies are much easier to standardize in terms of dosing, scheduling, and administration; pharmaceutical companies offer an enormous amount of financial and human capital to back drug studies that cannot be matched by smaller device firms and granting agencies to back non-pharmacological studies; and once at steady state, drugs can exert their influence all 168 h of every week, rather than the handful of hours (at most) that are usually devoted to nondrug interventions. On the other hand, drugs have disadvantages that include more potential for side effects and drug-drug interactions, never mind the general neural inhibition mediated by many spasticity drugs (sedating effects).

The tissues targeted by different anti-spasticity medications vary. While it is not the muscles, the neuromuscular junctions, nor the peripheral nerves that are the site of pathology in SCI, they are often selected for pharmaceutical intervention, in part because they are more accessible than the CNS, and the functional effect can be similar. In some ways, however, this is adding insult to injury, further weakening a damaged nervous system rather than addressing the problem at the site of pathology. Dantrolene, botulinum toxin, and phenol injections weaken muscles, block neuromuscular junctions, and preclude peripheral nerve signal conduction, respectively, and thereby weaken spastic muscles. While decreasing the effects of

abnormal motor output, however, they also diminish the capacity for more physiologically appropriate motor production and thereby theoretically limit recovery. We feel these are best used either as add-on medications when others directed at CNS circuitry have failed or when botulinum toxin injections are targeted at a specific, overly active muscle or sub-portion of a muscle that is reliably perturbing a specific motor function (discovered perhaps through poly-electromyography applied during specific tasks).

Pharmacological agents that address CNS neural circuitry are more directed toward reimposing inhibition at the site of pathophysiology in SCI. Nevertheless, the use of these medications may resemble using a sledgehammer as a fly swatter, as none of the medications are precise enough. It is nearly impossible to use these agents to impact just the altered neural circuitry leading to hyperreflexia or hypertonia or disordered coordination between motoneuron pools (dyssynergias) without also decreasing physiologically appropriate motor output. Whether we are talking about pre- or postsynaptic inhibition or action at GABA A, GABA B, alpha, 5HT, or dopamine receptors, drugs like benzodiazepines, baclofen, tizanidine, cyproheptadine, or dopamine agonists (respectively) should be used at minimally effective doses for the individual patient to best improve functional status. There is clinical experience, if not randomized clinical trials, to suggest that combinations of these drugs may be as or more effective than high doses of just a single line of pharmacological attack.

To better deliver drug to the site of impaired neural circuitry, baclofen can be given intrathecally instead of orally [99]. Intrathecal delivery trials can be pursued to ascertain clinical effect prior to the permanent implantation of an intrathecal pump, but it seems this course of action is often pursued before a full exploration of the effect of oral medication combination therapy. While intrathecal pumps can be very effective, and appeal to many with difficult to control spasticity, there is a rare but real risk of life-threatening baclofen withdrawal syndrome due to pump failure, disconnection, or poor management. All should be aware that pruritus in the absence of a rash in an intrathecal baclofen user is withdrawal until proven otherwise and that oral replacement is often insufficient in these cases. If it is not feasible to reestablish intrathecal delivery quickly (risk of infection with pump pocket abscess, for instance), intravenous benzodiazepine therapy may be necessary to stabilize the baclofen withdrawal patient.

One advantage to intrathecal delivery of baclofen is that it can be combined with intrathecal delivery of medications for neuropathic pain such as opioids, clonidine, and local anesthetics ("-caines") [100, 101]. This raises the issue of the interaction between pain and spasticity. Many patients use changes in their spasticity as an indication of other noxious stimuli or pathology they cannot consciously feel. Certainly, both muscle afferents and cutaneous nociceptive afferents can activate involuntary motor output in SCI, so conjunctively treating pain and spasticity in parallel makes sense. In patients taking gabapentin or pregabalin for chronic pain, they often report improvements in spasticity. When necessary, a urinary tract infection associated with worsened spasms should be treated not only with antibiotics but

also with a short course of increased pain medication along with a short-course increase in anti-spasticity medication dosing.

13.3.3 Electromagnetic Stimulation

Some electromagnetic stimulation paradigms are hailed as panaceas for pain, spasticity, and motor skills, but as with most non-pharmacological interventions, the evidence lags the hype. This is partly due to the infinite number of stimulus parameters that may be applied, leading to difficulty in comparing results from numerous small studies using different paradigms. We will briefly touch on several popular (or promising) electromagnetic interventions:

Transcutaneous electrical nerve stimulation (TENS) TENS units were developed to treat pain based on gate control theory [102]. However, once the FDA approved TENS unit marketing for home use, TENS use became widespread for weakness and spasticity as well. A typical TENS session comprises ~30–60 min of ~100 Hz stimulation at an intensity above sensory but below motor threshold [103]. The unit is usually placed over peripheral nerves serving the affected muscles but sometimes is placed directly over the affected muscles. When subjected to formal systematic review in multiple sclerosis, TENS failed to show benefit for spasticity [104]. However, many smaller studies in SCI and stroke have shown positive results [103, 105–108]. The mechanism of its effect in spasticity is not well understood [102, 109]. Regardless, given its safety profile and relatively affordable price, TENS will remain a popular non-pharmacological treatment option for the foreseeable future.

Functional electrical stimulation (FES) This methodology has been developed for decades to enhance volitional muscle control to achieve functional tasks of daily living by externally stimulating the appropriate nerves in the appropriate sequence [110]. Widely used FES-cycling systems allow individuals with SCI to more easily obtain cardiovascular workouts [110, 111]. However, FES recruits motor units in an unnatural sequence that results in clumsy, easily fatigued muscle responses [111, 112] (see chapter 24). This easy fatigability remains a fortuitous side effect in the context of spasticity, as fatigued muscles are less likely to spasm [7, 113–116].

At a more fundamental level though, by targeting peripheral nerves, FES bypasses all of the intrinsic circuitry that the central nervous system has evolved to carry out movements in the most efficient and coordinated manner. Successful modeling has not yet been achieved to recapitulate all of the feedback and feedforward loops that regulate groups of synergistic agonists and antagonists, that stabilize proximal muscle groups while distal muscles execute fine tasks, and that adjust movements in response to incoming sensory information. Whether human technology can outdo millions of years of evolution within the next several decades remains to be seen.

Transcranial magnetic stimulation (TMS) As opposed to stimulating directly over affected muscles, repetitive TMS (rTMS) targets cerebral origins of altered motor control. At pulse frequencies of 1–5 Hz, rTMS negatively modulates underlying cortical excitability, whereas at 5 Hz or greater, rTMS positively modulates underlying cortical excitability [117]. At excitatory frequencies, rTMS has been shown to reduce spasticity in SCI, multiple sclerosis, and cerebral palsy populations, presumably through increasing descending inhibitory drive to inhibitory interneuronal circuits [118–123]. Interestingly, although clinical spasticity and reciprocal inhibition improve in response to rTMS, H-reflex amplitudes do not consistently normalize in these studies [119, 121]. Conversely, inhibitory 1 Hz rTMS was shown to increase H-reflex amplitude, further supporting a model in which temporarily reducing descending cortical drive increases spinal cord hyperexcitability [118, 122]. Thus, multiple sessions of excitatory rTMS hold promise not only for reducing spasticity in SCI but also for improving motor control once appropriate combinations with other forms of activity-based therapies are found.

Direct current stimulation (DCS) This technique uses almost imperceptibly low current intensity, but it has had an outsized impact in numerous disease and performance-enhancing contexts – spasticity included [124–128]. The low-intensity current is far below action potential threshold, but given with the anode over the targeted site (either transcranial or transspinal), DCS seems to modulate neuronal membrane excitability in a serotonin- and NMDA-dependent manner [129–131]. However, several major gaps in mechanistic understanding persist: there is no technique to directly map how the low-energy current distributes within the body or to determine how individual variations in injury characteristics affect that distribution. Furthermore, the continuous nature of DCS makes it difficult if not impossible to elucidate timing-dependent synaptic changes. Therefore, although DCS has shown therapeutic benefit in spasticity and other contexts, its underlying mechanisms are quite likely to remain a black box.

Spinal cord stimulation An increasing number of groups are studying electromagnetic stimulation over the cord, which in our opinion is the most rational target for modulating spasticity. The first indication that spinal cord stimulation could relieve spasticity came after the advent of epidural spinal cord stimulators that had been designed for pain relief via gate control theory [132]. Epidural spinal cord stimulators were then fortuitously noted to relieve spasticity symptoms in multiple sclerosis patients [133, 134]. Since that time, expanding work has shown benefits not just for pain and spasticity but for improved volitional control as well [135–139]. Noninvasive spinal stimulation, delivered either via phasic or continuous direct current, has shown similar promise without the surgical risk or expense, making it a more attractive candidate for widespread application [53, 139, 140].

Both invasive and noninvasive spinal cord stimulation appear to activate local afferent circuits that trans-synaptically amplify signals transmitted along spared descending fibers. The cited studies have applied stimulation at various sites along

the cord, in patterns ranging from constant direct current to pulsatile frequencies between 10 and 1500 Hz. When targeted caudally to a lesion to combat lower extremity spasticity, frequencies of 50–100 Hz applied to the upper lumbar region are most effective, whereas frequencies of 20–60 Hz most effectively engage the locomotor CPG [139].

It remains to be seen whether a "sweet spot" can be found in which stimulation simultaneously reduces spasticity and enhances volitional motor control over multiple muscles or whether stimulation patterns will need to be dynamically adjusted depending on the task being performed. However, its ability to facilitate proper functioning of excitatory and inhibitory circuits simultaneously in their naturally intertwined milieu imparts spinal cord stimulation with extraordinary potential to improve all aspects of motor control after CNS injury.

13.4 Conclusion and Needs in the Field

Despite intense study for centuries, nervous system function and malfunction remain very poorly understood. Spasticity is no exception. The field has basic needs: better clinical and physiological assessment, better electrophysiological understanding, and, of course, better treatment. These are all inextricably linked.

The fact that SCI characteristics vary among human individuals makes things more complicated on the surface, but this variation also holds the key to better understanding. Potential correlations between spasticity phenotype and injury structure and physiology remain largely unstudied. Development and rigorous analysis of more relevant animal models could provide invaluable insight into the links between structure, function, and spasticity that would not be possible in human patients.

In humans, quantitative electrophysiological studies need to be melded with quantitative magnetic resonance imaging and clinical characterization of each individual's SCI phenotype. Obviously, this will require standardized, quantitative clinical spasticity assessments with properly curated metadata stored in public data repositories with consensus de-identification methods and public usage protocols.

Once the assessment and data repository infrastructure is in place, then "big data" algorithms should be able to exponentially improve our understanding of how SCI phenotype correlates with SCI structure and physiology. Incidentally, there has been (and likely always will be) much more study devoted to spasticity after stroke and multiple sclerosis than after SCI. Further studies need to specifically attend to unique features of SCI spasticity, and why they differ from features of other types of spasticity.

Thus, spasticity needs to be rebranded – the perception of spasticity as nervous system hyperactivity needs to be replaced with a more physiologically appropriate perception as an altered state of motor control. With this mindset, we are optimistic that future interventions providing individually customized combinations of patterned, circuit-specific activation should be able to simultaneously improve both spasticity and motor control.

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Cardiovascular Dysfunction Following Spinal Cord Injury

14

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Abstract

Cardiovascular issues following spinal cord injury (SCI) are of paramount importance considering they are the leading cause of death in this population. The disruption of autonomic pathways leads to a highly unstable cardiovascular system, with impaired blood pressure and heart rate regulation. In addition to low resting blood pressure, on a daily basis, the majority of those with SCI suffer from transient episodes of aberrantly low and high blood pressure (termed orthostatic hypotension and autonomic dysreflexia, respectively). In fact autonomic issues, including the resolution of autonomic dysreflexia, are frequently ranked by individuals with SCI to be of greater priority than regaining motor function. Due to a combination of these autonomic disturbances and a myriad of lifestyle factors, the pernicious process of cardiovascular disease is accelerated after SCI. Unfortunately, these secondary consequences of SCI are only beginning to receive appropriate clinical attention. Immediately after high-level SCI, major cardiovascular abnormalities present in the form of neurogenic shock. After

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subsiding, new issues related to blood pressure instability arise, including orthostatic hypotension and autonomic dysreflexia. The present chapter reviews autonomic control over the cardiovascular system before injury and the mechanisms underlying cardiovascular abnormalities after SCI, while also detailing the end-organ consequences including those of the heart, as well as the systemic and cerebral vasculature. The tertiary impact of cardiovascular dysfunction will also be discussed, such as the potential impediment of rehabilitation, impaired cognitive function, and limitations to exercise capacity. In the recent past, our understanding of autonomic dysfunction has been greatly enhanced; however, it is vital to further develop our understanding of the long-term consequences of these conditions, which give us insight to cardiovascular disease morbidity and mortality in this population.

14.1 Introduction

Spinal cord injury (SCI) is a devastating condition with the capacity to change the trajectory of life resulting in increased morbidity and earlier mortality. Due to a combination of major autonomic disturbances and the related cardiovascular dysfunction, as well as a myriad of lifestyle-altering factors, the pernicious process of cardiovascular disease is extremely accelerated after SCI [1, 2]. Even after controlling for major risk factors, the risk of heart disease is almost threefold higher in those with SCI, while the risk for stroke is almost fourfold higher compared to those without SCI [3].

Disruption of the neuronal pathways of the spinal cord is well known to lead to paralysis, but also leads to major alterations of the autonomic nervous system. Although the site of injury to the spinal cord is generally localized to a small region (including neurons, supporting cells, as well as ascending and descending neuronal pathways), the effect of this disruption is frequently associated with a wide array of dysfunctions due to malfunction of the autonomic nervous system (see chapter 2).

Alterations in autonomic function are often dominated clinically by changes in spinal sympathetic control [4, 5]. Specifically, those with SCI often suffer from unstable blood pressure, including low resting blood pressure, severe drops in blood pressure when moving to the upright position (termed orthostatic hypotension (OH), and/or aberrant life-threatening bouts of acute hypertension termed autonomic dysreflexia (AD) [6]. The effect of SCI on autonomic/cardiovascular dysfunction is well reported in a variety of human and lower-order animal models (i.e., rodents) [6, 7].

Autonomic issues, such as cardiovascular dysfunction, are most frequently ranked by patients with SCI to be of greater priority to them than regaining their motor function [8]. Clinically, the importance of cardiovascular dysfunction is often overlooked and poorly understood and presents as part of complex and challenging clinical scenarios. In light of this, and the consideration that cardiovascular disorders in both the acute and chronic stages of SCI represent the most common causes

of death in individuals with SCI [9, 10], it is imperative to understand the cardiovascular consequences of this condition. It is only during the last decade, that in addition to the assessment of motor and sensory deficits [11], newly developed international Autonomic Standards were developed for clinical evaluation and management of autonomic dysfunctions following SCI [12].

The present chapter is focused on delineating cardiovascular dysfunction after SCI. Specific areas to be reviewed include: autonomic regulation of cardiovascular function, the underlying mechanisms of cardiovascular dysfunction after SCI, major cardiovascular clinical conditions after SCI such as orthostatic hypotension and autonomic dysreflexia, changes in cardiovascular disease risk factors and end-organ maladaptation after SCI, as well as management recommendations for SCI patients in order to mitigate cardiovascular dysfunction.

14.2 Autonomic Regulation of Cardiovascular Function

Arterial blood pressure and heart rate regulation are under constant control of the autonomic nervous system, which is comprised of two primary divisions: sympathetic and parasympathetic (Fig. 14.1) [14, 15]. Activation of the sympathetic nervous system plays an excitatory role (i.e., fight or flight response) and results in an increase in sympathetic peripheral nerve activity leading to increased heart rate, increase in cardiac contractility, and generalized systemic vascular constriction; together leading to increased arterial blood pressure. On the other hand, activation of the parasympathetic nervous system typically is limited to reducing heart rate and cardiac contractility (via vagal nerve), and is widely accepted to not extend to the vasculature itself, except in specific regions including blood vessels of the salivary glands, gastrointestinal glands, genital erectile tissue, and potentially the cerebrovasculature [16–18].

Although some cortical areas and hypothalamic regions [4] with tonic and inhibitory influences on cardiovascular functions have been identified, it is medullary neurons within the rostral ventral lateral medulla that are considered to be the major sympathetic cardiovascular regulatory region responsible for maintenance and regulation of blood pressure [19]. These sympathetically active central neurons project to the spinal cord and travel primarily through the dorsolateral funiculus synapsing on the spinal sympathetic preganglionic neurons (SPNs), which are located predominately within the lateral horns of spinal gray matter in spinal segments T1–L2. The axons of SPNs (preganglionic fibers) exit the spinal cord via ventral roots and synapse on the sympathetic ganglionic neurons within paravertebral chain ganglia (ganglionic neurons) [20]. Finally, the postganglionic neurons innervate target organs such as blood vessels (adrenergic sympathetic innervation), sweat glands, and piloerectors (cholinergic sympathetic innervation) [20]. Both the central and peripheral autonomic nervous systems provide crucial coordinated regulation of the cardiovascular system in order to provide appropriate blood pressure throughout daily living including such activities as exercise and orthostatic challenges.

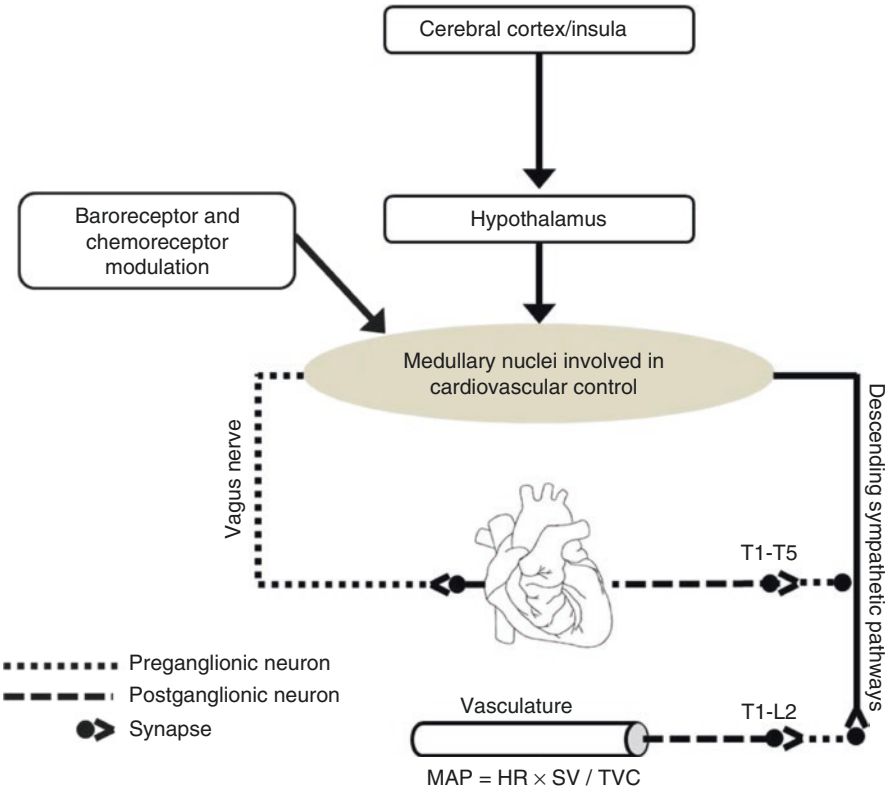


Fig. 14.1 Autonomic cardiovascular control. The cerebral cortex and hypothalamus project to the nuclei of the medulla oblongata, where autonomic cardiovascular control is coordinated and integrated with input from baroreceptors, chemoreceptors. Parasympathetic control of cardiovascular systems exits at the level of the brainstem via the vagus nerve. The preganglionic fibers of the vagus nerve then synapse with postganglionic parasympathetic neurons in ganglia on or near the target organ. Descending sympathetic pathways provide tonic control to sympathetic preganglionic neurons (SPNs) involved in cardiovascular regulation. Cell bodies of SPNs are found within the lateral horn of the spinal cord in segments T1–L2 and exit the spinal cord via the ventral root, and they then synapse with postganglionic neurons located in the sympathetic chain (paravertebral ganglia). Finally, the sympathetic postganglionic neurons synapse with target organs such as the heart and blood vessels. Considering Poiseuille's law, blood pressure is affected to the fourth power by arterial diameter and only linearly by increases in flow [heart rate (HR)-derived changes in cardiac output]. As such, it is not surprising that the vasomotor branch of the baroreflex is much more important than the vagal branch for the maintenance of mean arterial blood pressure (MAP). *TVC* total vascular conductance, *SV* stroke volume (Modified from Phillips et al. [13])

In terms of the parasympathetic division, the vagal nerve exits the central nervous system supraspinally and reaches target organs such as the heart and cerebral blood vessels without traversing the spinal cord. The parasympathetic division plays an important role in dynamically regulating the heart rate over very short time frames of 2–3 s [21], but does not play a major role in steady-state blood pressure

either in a supine or upright position [22]. Some sacral parasympathetic cell bodies of the parasympathetic division are located in the spinal segments S2–S4; however, they do not play a role in cardiovascular control. Both sympathetic and sacral parasympathetic preganglionic neurons receive supraspinal tonic and inhibitory nervous system control via spinal autonomic pathways that [23, 24], unfortunately, are frequently disrupted after SCI [25].

The baroreflex is the primary mechanism responsible for short-term regulation of blood pressure [13, 26] and also plays a critical role in long-term blood pressure regulation [27]. The baroreflex is comprised of two interdependent systems [28, 29] that work in concert as one reflex system. The first, a low-pressure system, is made up of cardiopulmonary stretch receptors located in the heart and lungs, which augments sympathetic nervous system activity in response to reductions in central venous pressure and volume [30]. The second, a high-pressure baroreflex system, consists of stretch receptors located in the tunica adventitia of the aortic arch and carotid bulbs [31]. These spray-like nerve endings generate a more rapid rate of depolarization and hence increase the frequency of action potentials in afferent nerves during periods of increased wall distension [30]. The signal is transmitted from the carotid bulb via the glossopharyngeal nerve (vagal nerve) and the aortic arch via the vagal nerve to the nucleus of the solitary tract in the medulla oblongata [14]. This transmission, which provides surrogate information on systemic blood pressure, is integrated with other afferent information (such as chemoreceptor afferent signals) in order to modulate efferent nervous activity transmitted through the vagal nerve and sympathetic system to target organs, with the aim of rapidly maintaining blood pressure around a set point (Fig. 14.1) [30]. For example, when a human moves from the supine to upright position, approximately 500 ml of blood is translocated away from the heart and brain and toward the blood vessels of the gut and legs [32]. Central baroreceptors detect reductions in stretch and respond by decreasing vagal tone to the heart and increasing peripheral sympathetic activity. The increase in sympathetic tone results in an increased heart rate and peripheral vasoconstriction that is responsible for maintaining stable arterial blood pressure [13]. After SCI, although the baroreceptors certainly detect reductions in central blood volume during orthostasis, disrupted descending sympathetic pathways precludes the capacity to vasoconstrict, often resulting in abnormal fluctuations in blood pressure with changing body position [13]. Our most recent understanding, as well as mechanistic insight, surrounding these episodes and other cardiovascular conditions after SCI will be discussed in the following sections.

14.3 Mechanisms Underlying Abnormal Cardiovascular Control Following SCI

We are just beginning to unravel the mechanisms underlying abnormal cardiovascular function after SCI. Due to the lack of a suitable animal model of OH, most mechanistic studies have focused on AD as the clinical condition of interest. The morphological changes within the spinal autonomic circuits after SCI have been

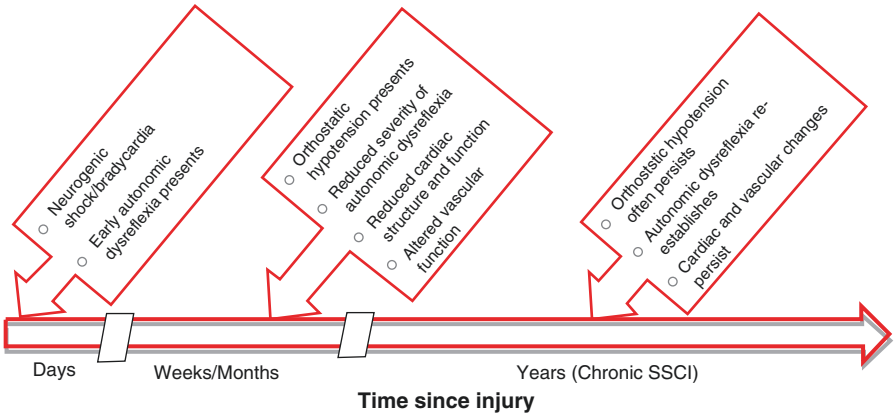


Fig. 14.2 Timeline of changes in autonomic and cardiovascular function after spinal cord injury

established relatively recently [33]. Furthermore, the role these changes are playing in the development of autonomic dysfunction has only just been solidified [34–36]. A variety of autonomic circuits have been highlighted that possibly contribute to abnormal cardiovascular control after SCI [6]. The disruption of descending spinal cardiovascular pathways leads to a minimum of six neuroanatomical changes that influence autonomic cardiovascular control:

1. Initial sympathetic hypoactivity due to loss of supraspinal tonic sympathetic excitation [37, 38].
2. Alterations in the morphology of sympathetic preganglionic neurons (SPNs) [20, 33].
3. Plastic changes of the spinal circuits (i.e., dorsal root afferent sprouting, potential formation of aberrant synaptic connections [39], or aberrant inputs to the spinal interneurons) [34].
4. Altered sympatho-sensory plasticity [35].
5. Altered peripheral neurovascular responsiveness [40].
6. Cumulative effect of tertiary factors. These factors will be discussed below.

Autonomic Pathways and SPN Plasticity It is now appreciated that in the acute stage after SCI, SPNs atrophy. However, over time, they regain somewhat normal morphology (similar soma size as pre-injury but more dendritic arbor and aberrant connections) [15]. It is most likely that the loss of descending projections of medullary neurons result in the initial atrophy of SPNs, as many of these are thought to synapse directly. In the very early phase after SCI, loss of descending inhibitory pathways predisposes individuals to early AD episodes, while, later atrophy of SPNs leads to an intermediate period where AD is less severe (Fig. 14.2) [15]. Disrupted descending pathways, as well as atrophied SPNs, likely contribute to the lack of sympathetic tone and very low resting blood pressure in the early phase of

injury as well as the extremely high prevalence of OH. As the phase of injury transitions into the more chronic stage, AD manifests again [6, 41]. For example, AD is most commonly documented during the subacute and chronic stages of SCI. AD often becomes clear within 2–3 months after SCI in those with SCI above the T6 spinal segment [42].

Dorsal Afferents and Intraspinal Plasticity Exaggerated sensory input to the spinal cord occurs caudal to the site of injury after SCI. For example, evidence from animal studies suggests that dorsal root afferents sprout along with an enlargement of soma size in the dorsal root ganglia after SCI [39, 43, 44]. Specifically, there is an intrusion of calcitonin gene-related peptide immunoreactive (CGRP+) afferent fibers further into the spinal cord (quantified as increased CGRP+ fibers in laminae II–V post-SCI) (see chapter 2) [45], accompanied by somal hypertrophy of the transient receptor potential cation channel subfamily V member 1 (TRPV1) in the dorsal root ganglia [35]. It is likely that primary afferents such as CGRP+ axons in the dorsal root ganglion sprout and extend from their proper location (laminae I–II) (see chapter 2) [15]. Increased sprouting of primary afferents would generate new intraspinal circuits [34] and is a suspected mechanism for AD due to both similar time courses [34, 45–47] and its relation to AD severity [48].

Vasculature Peripheral Component An additional autonomic alteration associated with AD after SCI includes hyperresponsiveness of blood vessels to alpha-adrenergic stimulation. Specifically, it has been shown that the mesenteric artery is hyperresponsive to the pressor agent phenylephrine in rodents after SCI due to increased sensitivity secondary to impaired neuronal reuptake [49, 50]. Furthermore, a number of studies have shown exaggerated pressor responses to alpha sympathomimetic administration [51–53]. It has also been shown that sympathetically correlated spinal interneurons are hypersensitive to afferent stimuli after SCI [14, 15, 34]. Together, the combination of hyperresponsive interneurons and vascular smooth muscle, as well as the increased influence from primary afferents, creates a "perfect storm" of reorganization predisposing to episodes of transient hypertension in response to nociceptive or non-nociceptive afferent stimulation (i.e., AD). It is interesting to highlight however the multifaceted contributions to the presence of AD. For example, reductions in AD severity have been shown after interventions showing no reduction in blood vessel hyperresponsiveness [49], suggesting other factors such as altered sympatho-sensory plasticity may be playing a more central role.

Clearly, there are a number of factors after SCI that predispose to the frequent and widespread occurrence of AD and OH, which are major clinical conditions after SCI affecting both the quality and quantity of life in this population.

14.4 Cardiovascular Consequences Following SCI

Over the past 10 years, our knowledge regarding the underling pathophysiology of autonomic dysfunction after SCI has been enhanced greatly [5, 34, 41, 54]. The most prominent outcomes of mechanistic maladaptations described above are low

resting blood pressure [6] as well as extremely labile blood pressure characterized by frequent episodes of low blood pressure when assuming an upright position (OH) and episodes of high blood pressure in response to afferent stimuli below the level of injury (AD). These cardiovascular conditions will be discussed in detail throughout the next sections.

14.4.1 Low Resting Blood Pressure

In addition to hypotension during the acute period following SCI (neurogenic shock, see below) individuals with high thoracic and cervical SCI frequently experience low arterial blood pressure at rest that is notably lower than in able-bodied individuals [55]. Clinical evidence indicate that the extent and severity of hypotension, correlates well with the level and severity of SCI (Fig. 14.3) [41, 56–58]. Analysis derived from the non-SCI population has clearly illustrated that an inverted-U relationship exists in terms of resting blood pressure, whereas in addition to high blood pressure, there are significant clinical conditions associated with having a blood pressure that is too low [59–61]. This has recently been corroborated in the SCI population, where impaired cerebrovascular and cognitive function has been shown to be associated with low resting blood pressure [62]. In the SCI population, low resting blood pressure is also associated with a number of conditions, including cognitive impairment, exacerbated dizziness, and the development of syncope, as well as poor mood, lethargy, and fatigue [63–67]. Following this, low blood pressure should be appreciated and addressed in those with SCI.

14.4.2 Autonomic Dysreflexia

Episodes of AD are characterized by an acute elevation of systolic blood pressure of at least 20 mmHg, which may or may not be accompanied by a decrease in heart rate [68], and occurs in response to peripheral painful or non-painful visceral or somatic stimulation below injury, including a full bladder or bowel (see Fig. 14.4 for example of AD during bladder filling). It is now well appreciated that AD episodes can occur in both the acute and chronic phases of SCI [42, 69]. In fact, episodes of AD, where systolic blood pressure can rise above 300 mmHg, are now known to occur up to 40 times/day (average of 11 times/day) in the majority of those with high-level SCI above the T5 level [70]. Episodes of AD are often accompanied by a pounding headache, and flushing above the injury [6, 68, 71]. Left untreated, episodes of AD could result in life-threatening complications (Table 14.1) including cerebral hemorrhage, retinal detachment, seizures, cardiac arrhythmias, and death [152–154].

The most common stimuli to trigger AD include bladder and bowel distention, but can also be brought on by spasms, pressure sores, and even something as simple

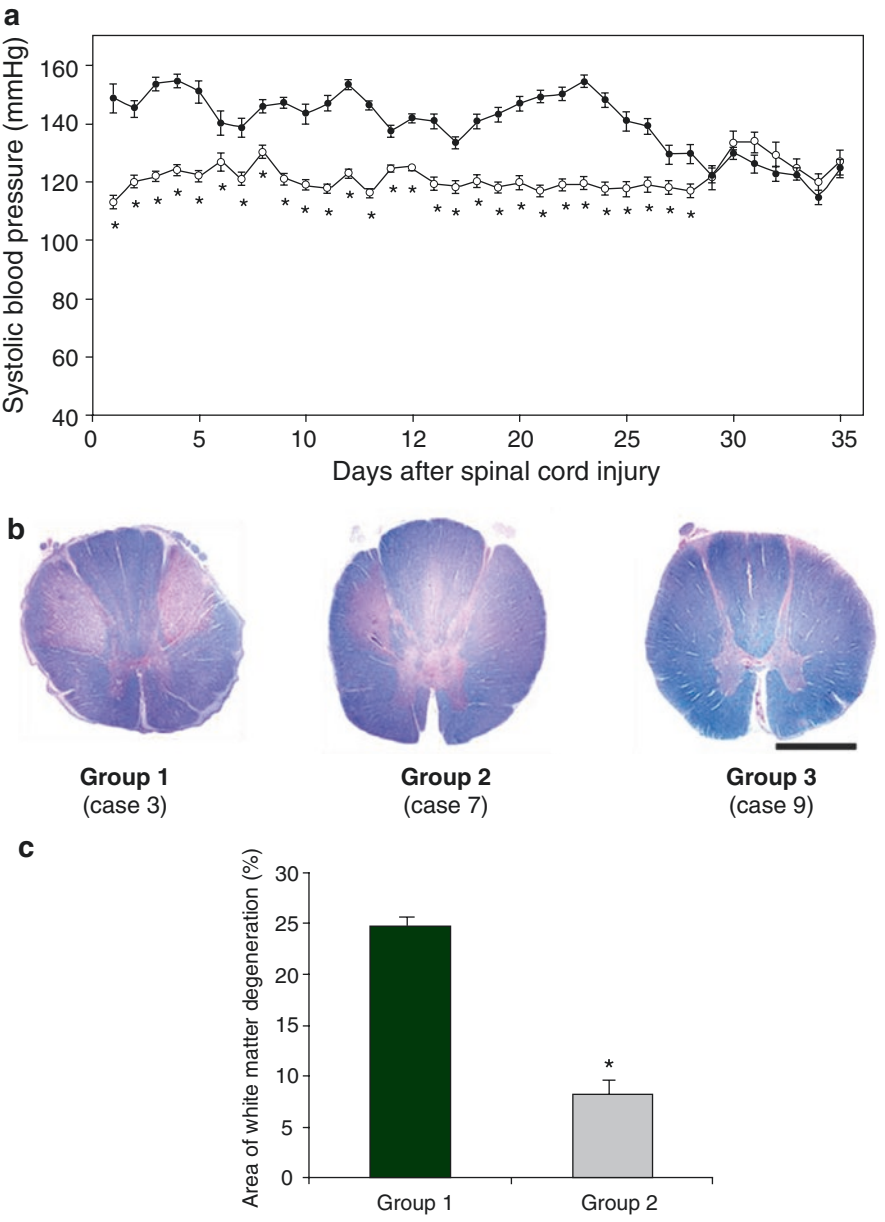


Fig. 14.3 Illustrating the effect of completeness of injury on blood pressure stability. Groups *1*, *2*, and *3* represent the same groups of participants from Parts (a), (b), and (c). Part (**a**): Daily mean ± standard error of systolic blood pressure from days 1 to 35 after spinal cord injury (SCI). Patients with severe cardiovascular complications (*empty circles*, Group *1*) were compared to those not developing major cardiovascular complications (*filled circles*, Group *2*) and were significantly different. Part (**b**): Sections of postmortem human spinal cord tissue stained for myelin with Luxol fast blue from representative cases of Group *1*, Group *2*, and Group *3* (non-SCI controls). Part (**c**): Areas of significantly more extensive axonal degeneration (pink areas within gray white matter) are present in individuals from Group *1* as compared to Groups *2* or *3*. *Represents $P < 0.05$) (Modified from Furlan et al. [25])

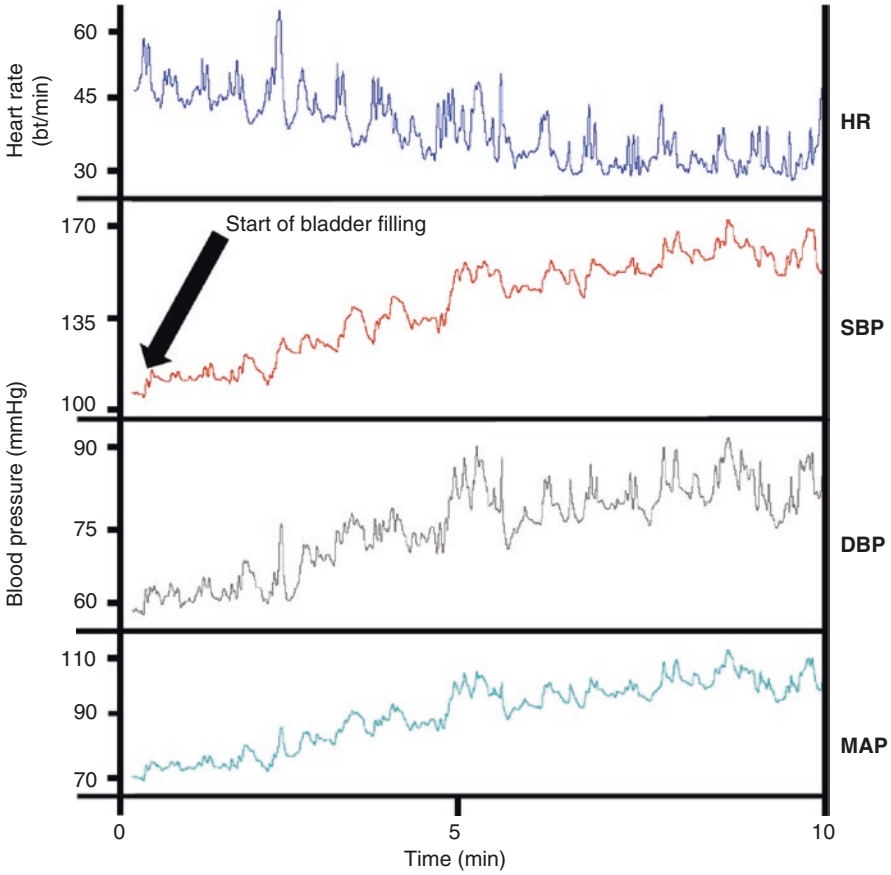


Fig. 14.4 Continuous beat-by-beat changes in heart rate as well as systolic, diastolic and mean blood pressure (*SBP*, *DBP*, *MAP*) during autonomic dysreflexia induced by urodynamic bladder filling in one male with a T2 motor complete (AISA) spinal cord injury. Clinical observation from our laboratory. Note that SBP increases by 70 %, up to 170 mmHg

as a tight shoelace [5]. Catheterization and manipulation of an indwelling catheter can also lead to AD, in addition to urinary tract infection, detrusor-sphincter dyssynergia, and bladder percussion. There are also a number of iatrogenic triggers such as cystoscopy, penile vibrostimulation or electrostimulation for ejaculation, as well as the electrical stimulation of muscles [89, 96, 155]. The intensity of AD episodes is variable, and not all episodes are severe, especially if the triggering stimulus is resolved promptly. In fact, many AD episodes are asymptomatic (i.e., patient does not recognize it even though blood pressure is increasing) or characterized by sweating and/or piloerection alone [156]. The level and completeness of the injury are the critical determinants for the presence of AD which is three times more common in complete versus incomplete quadriplegics [157] and typically occurs

Table 14.1 Triggers and conditions associated with autonomic dysreflexia

Urogenital system
Bladder distension [72–77]
Urethral distention [78–81]
Urodynamics/cystoscopy [72, 76, 78, 82–84]
Urinary tract infections [79, 85–87]
Epididymitis [88]
Renal calculus [89, 90]
Electroejaculation [91–93]
Coitus [94, 95]
Penile stimulation to obtain reflex erection [96–98]
Vaginal dilation [99]
Uterine contractions [77, 100–105]
Testicular torsion
Gastrointestinal system
Bowel distention [76, 106, 107]
Anal fissures/hemorrhoids [99, 108, 109]
Esophageal reflux [110]
Enemas [111]
Gastric dilatation [99]
Gastric ulcer [112]
Acute abdomen (peritonitis, cholecystitis, appendicitis) [112]
Skin/musculoskeletal
Cutaneous stimulation [113, 114]
Sunburns [115]
Pressure sores [116, 117]
Ingrown toenails [76]
Functional electrical stimulation [118]
Spasticity [119]
Bone fractures [120, 121]
Intramuscular injection [122]
Hip instability [123, 124]
Surgical procedures/conditions
Surgical procedures [125–130]
Radiologic procedures [131]
Unstable fusion [132]
Lumbar spondylolisthesis [133]
Miscellaneous
Pulmonary embolism [134]
Range-of-motion exercises [135]
Position changes [136, 137]
Medications [74]
Emergence in cold water [138]
Acupuncture [139]

(continued)

Table 14.1 (continued)

Advantages of autonomic dysreflexia (AD)
Self-induced AD (intentional boosting) [140–142]
Signal of onset of serious medical complications [99, 112]
Complications of AD seizures [88, 143]
Retinal hemorrhages [82, 88]
Intracranial hemorrhage [88, 125, 144–146]
Transient aphasia [147]
Neurogenic pulmonary edema [148]
Cardiac arrhythmias [71, 149]
Cardiac arrest [150]
Death [88, 125, 151]

primarily when the SCI is at or above the T6 spinal segment (see chapter 2) [5, 41]. As discussed previously in this chapter, changes in the autonomic circuits in the spinal cord are major contributing factors to the development of AD [34].

Finally, it should be noted that, although AD is certainly a life-threatening emergency [125] and known to be unpleasant [94], some individuals with SCI voluntarily induce AD in order to increase their blood pressure, as it may in some cases improve their athletic performance [140]. The inducement of AD is referred to as "boosting" and is considered unethical and illegal by the International Paralympics Committee Medical Commissions, leading to medical examinations before competitions. The occurrence of boosting in competition is a testament to the devastating functional and performance limitations imposed by the autonomic cardiovascular dysfunctions present after SCI.

14.4.3 Orthostatic Hypotension

Episodes of OH are characterized by substantial declines in blood pressure when assuming the upright posture (Fig. 14.5). After SCI, the interruption of sympathoexcitatory pathways from the brainstem to the SPNs impairs the efficaciousness of the arterial baroreflex to cause vasoconstriction and maintain blood pressure [158, 159]. Although the cardiovagal baroreflex is impaired after SCI, it is the sympathetic system that is primarily responsible for blood pressure maintenance following the first 2–3 s of orthostatic challenge (before which the cardiovagal response is important) [13]. The result is both low venous return secondary to blood pooling in the vasculature caudal to the site of injury, as well as low arterial blood pressure/vessel tone [13]. Additionally, there are low resting catecholamine levels after cervical SCI and no discernable increase with central supraspinal sympathetic activation induced by upright tilt [7]. The presence of stiffer central arteries (which are responsible for detecting changes in blood pressure) after SCI further impairs baroreflex sensitivity [1]. Orthostatic hypotension is most

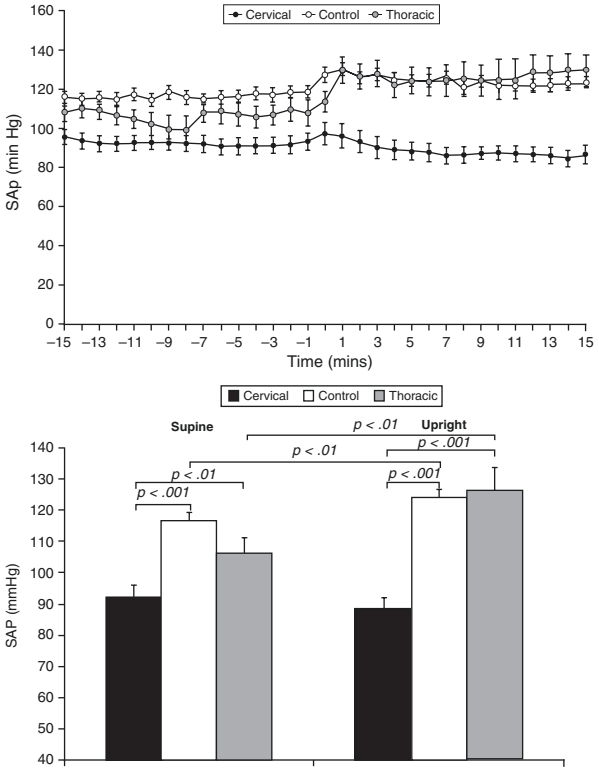


Fig. 14.5 Changes in systolic arterial blood pressure (*SAP*) during passive sit-up test in cervical SCI patients, non-injured controls, and thoracic SCI patients. *Top*: mean ± standard error SAP recorded every minute. The *black line* represents the upright portion of the sit-up test, while prior to that patients were supine. *Bottom*: mean ± standard error SAP averaged from the entire supine or upright portion of the sit-up test (Modified from Claydon et al. [63])

common and severe in the acute phase of SCI, but also can be observed in the chronic phase among individuals with high cervical injuries [66, 160]. Similar to resting blood pressure, the severity and level of injury to descending cardiovascular autonomic pathways is directly associated with OH (Fig. 14.5) [7]. Together, this indicates that the extent of cardiovascular instability after SCI is related to the completeness of injury to autonomic pathways within the spinal cord. Clinically, OH is defined as a decrease in systolic blood pressure of 20 mmHg or more, or a decrease in diastolic blood pressure of 10 mmHg or more, when assuming an upright posture from the supine position, regardless of presence of symptoms [161]. This definition was agreed upon by the Consensus Committee of the American Autonomic Society and the American Academy of Neurology [161]. Presyncopal symptoms after SCI are no different from the able-bodied population [162]. These include light-headedness, dizziness, blurred vision, fatigue, nausea,

dyspnea, and restlessness [163, 164]. Orthostatic hypotension is extremely common in those with SCI. For example, one study showed that OH occurs in up to 74 % of individuals with SCI when performing orthostatic maneuvers during physical therapy and mobilization [67]. Similar to AD, OH does not always lead to presyncopal symptoms, and many individuals have asymptomatic OH. In fact, 41 % of those with SCI were asymptomatic during episodes of OH [7]. Recently, we have shown that often OH persists into the chronic stage of SCI; however presyncopal symptoms may partially subside [7]. In terms of prevalence, in the chronic phase of SCI, OH occurs in up to 50 % of cervical SCI patients and 18 % of thoracic patients; however, from this OH-positive group, presyncopal symptoms were only present in one third and one fifth of individuals [7]. This finding suggests that tolerance to low blood pressure and cerebral perfusion pressure may improve with time after SCI [65, 165, 166]. Considering the association between OH and an elevated risk of stroke in the able-bodied population [167], as well as the fact that stroke risk is 3–4 times greater after SCI, it is logical to posit that the presence of OH after SCI plays a contributing role [3, 168].

Other factors contributing to the presence of OH after SCI include reduced plasma volumes caused by hyponatremia [163], insufficient increases in the efficaciousness of the renin-angiotensin system to maintain blood pressure [51], and potential cardiac deconditioning [169–171]. A similar contribution from these mechanisms leads to low resting blood pressure after SCI as well [6].

To summarize, episodes of OH can lead to syncope, nausea, fatigue, and dizziness and significantly impede rehabilitation. Over the long term, OH likely contributes to an elevated risk of stroke after SCI. Resting hypotension also plays a role in cognitive dysfunction by exacerbating the severity and frequency of orthostatic intolerance. Approaches to combat the abnormal cardiovascular responses after SCI are only in the early stages of development and will be discussed below.

14.5 Cardiovascular Changes with Time Following SCI

Spinal cord injury results in a number of acute and chronic alterations in physiology and behavior that together contribute to cardiovascular decline over the life-span of individuals with SCI (Fig. 14.2). This section will discuss acute and chronic conditions after SCI and considerations related to cardiovascular decline that contribute to the high risk of developing cardiovascular diseases in this population.

14.5.1 Acute Cardiovascular Changes

It is clear at this point in the chapter that cardiovascular function itself is critically compromised by SCI. In the acute phase following high level of SCI, individuals present with severe hypotension and bradycardia [6]. These two issues are classic characteristics of the condition known as neurogenic shock [172]. Up to 100 % of

individuals with cervical SCI will experience severe hypotension in the acute phase after SCI, and roughly 50 % will require vasopressive therapy to maintain arterial blood pressure [6, 173]. Additionally, the majority of individuals with SCI will suffer from abnormal heart rates in the acute phase following SCI. Specifically, bradycardia has been reported in 64–77 % of patients with cervical SCI (being most severe for up to 5 weeks after injury) [82, 174–177]. When SCI occurs in the mid-thoracic region or caudally, bradycardia is typically less severe, secondary to partial preservation of supraspinal influences over cardiac sympathetic neurons. Neurogenic shock has the potential to significantly impact long-term recovery from SCI, by delaying acute surgical management of the injury itself [178], and the arrhythmias that present during this phase of injury can require the implantation of a cardiac pacemaker [176, 177].

It is important to differentiate the terms "neurogenic shock" and "spinal shock," both of which can occur during the acute phase of SCI, but represent two different conditions altogether [57, 179]. Although these terms are often used interchangeably, neurogenic shock describes the clinical outcomes of changes in autonomic blood pressure control after SCI, while spinal shock describes the clinical outcomes of changes in motor/sensory/reflex function after SCI (i.e., flaccid paralysis and areflexia) [179].

14.5.2 Long-Term Cardiovascular Considerations

14.5.2.1 Contributing Factors

It has been relatively recent that cardiovascular diseases were identified as the primary cause of death after SCI [10, 180]. In addition to the aforementioned lability in blood pressure (i.e., frequent episodes of AD and OH), we now appreciate that a number of interacting secondary conditions occur after SCI which likely increases the trajectory of cardiovascular disease progression throughout a patient's life-span, including widespread physical inactivity [181, 182], type II diabetes [183–186], increased inflammation [187], suboptimal cholesterol profile [188], and accelerated arterial stiffening [1, 2]. Comprehensively reviewing these conditions is beyond the scope of this chapter; however the following sections will highlight these issues and management recommendations.

14.5.2.2 Physical Inactivity

In addition to increased mortality, reduced physical activity is related to a myriad of conditions including accelerating cardiovascular disease progression [189]. Those with SCI, due to a spectrum of physical and psychosocial conditions and barriers, are less physically active when compared to able-bodied peers [1, 190]. A number of studies have highlighted that physical inactivity in those with SCI is a critical mediating factor related to the propagation of subclinical prognosticators for cardiovascular disease development [191]. Recent clinical guidelines for physical activity recommend for individuals with SCI to engage in aerobic

exercise twice weekly for a duration of at least 20 min, at moderate-to-vigorous intensity for health improvements indicative of mitigated cardiovascular disease risk [192]. Previous to this, clinical guidelines from American College of Sports Medicine recommended 3–5 exercise sessions per week at 50–60 % of maximum aerobic capacity for 20–60 min [193].

14.5.2.3 Impaired Glycemic Control

Hyperglycemia is well known to lead to diabetes or prediabetes. These abnormalities are identified with elevated fasting glucose levels (≥7 mmol/L), an elevated routine (i.e., non-fasting) blood sugar with symptoms of diabetes (≥11.1 mmol/L) hemoglobin A1c (HbA1c ≥6.5 %), or with an abnormal glucose tolerance test (2 h post-75 g glucose ingestion ≥11.1 mmol/L; CDA, 2008). In those with SCI, the prevalence of abnormal glycemic control and diabetes itself is consistently higher than in the able-bodied population [186]. Exercise plays a role in mitigating glycemic abnormalities in those with SCI as well as able-bodied individuals. Although the majority of studies reported improvements in glycemic control due to exercise after SCI, the modalities employed required expensive equipment and experienced training personnel (i.e., functional electrical stimulation of paralyzed limbs, body weight-supported treadmill exercise of lower limbs) [194–196]. No well-established recommendations exist for the management of glycemic abnormalities after SCI, although effective monitoring and standard treatment are encouraged.

14.5.2.4 Inflammation

Chronic inflammation is a key propagating factor in cardiovascular disease progression [197]. The measurement of highly sensitive C-reactive protein (hs-CRP) can clinically quantify the presence and severity of inflammation, which is statistically speaking an independent risk factor for the development of cardiovascular disease [198]. There are frequent infections in the chronic phase of SCI, including urinary tract infections and decubitus ulcers [199]. Therefore, inflammatory markers may spuriously represent underlying infection and not chronic inflammation. It should be appreciated however that in those with SCI, hs-CRP as well as other markers of systemic inflammation are significantly elevated, even without acute infection [200, 201]. To date, there are no studies clearly linking chronic inflammation in those with SCI and the development of cardiovascular disease; however, considering the link in able-bodied individuals, it is highly likely that chronic inflammation plays an exacerbating role [197]. The current recommendations suggest close monitoring of inflammation in SCI; however, the management thresholds are not clearly established and likely should be based on able-bodied individuals in the absence of SCI-specific data.

14.5.2.5 Lipid Abnormalities

Following SCI, there is consistent evidence of lipid profile abnormalities, particularly reduced high-density lipoprotein, which is a well-established risk factor for cardiovascular disease development [188, 202, 203]. Most individuals require

pharmaceutical intervention in order to normalize suboptimal cholesterol profiles [204, 205], and the cardiovascular disease event reduction strategies have been adopted from other populations not suffering from SCI [205, 206]. A number of studies highlight that physical activity (either active lower body or functional electrical stimulation of the lower body) can play a role in normalizing lipid profiles in those with SCI [207–210]; however no clear guidelines exist.

Unfortunately, all of the above risk factors are exaggerated in those with SCI, and no specific guidelines exist for these risk factors (with the exception of physical activity). In light of this, in most cases, it is suitable to follow standard (i.e., able-bodied) monitoring and treatment for well-established cardiovascular disease risk factors [3].

14.5.3 Cardiovascular End-Organ Maladaptation

14.5.3.1 Arterial Dysfunction

A great deal of interest has stemmed recently from the assessment of arterial health (e.g., arterial pulse wave velocity, endothelial responsiveness), both from the perspective of measuring subclinical cardiovascular disease progression in research, as well as in clinical practice for the capacity of arterial markers to be powerful predictive tools for future cardiovascular disease events [191, 211]. Arterial health markers also incorporate cardiovascular disease risk that is not captured by standard clinical assessments such as Framingham scores [212, 213], suggesting that standard predictive tools do not accurately detect cardiovascular disease risk stemming from arteriosclerotic decline. A number of studies have examined arterial health and function in those with SCI [1, 2, 214, 215]. Currently, it appears that SCI elicits very little effect on endothelial function, although this is likely confounded by imprecise covariation for critical influencing factors such as a rapidly reducing arterial diameter post-injury, secondary to reduced metabolic blood flow requirements in downstream perfused tissue [216, 217]. Aortic stiffness, however, as measured using pulse wave velocity, is consistently elevated by 2–3 m/s in those with SCI as compared to able-bodied individuals [1, 2], which corresponds to a 28–45 % increased risk of age-, sex-, and risk factor-adjusted likelihood of total cardiovascular events, cardiovascular mortality, and all-cause mortality [191]. Additionally, increased central arterial stiffness is shown to be a major cause of cardiac dysregulation after SCI, with recent data suggesting vascular stiffening is the primary cause of cardiovagal baroreflex dysfunction in this population [214]. Although arterial stiffness is currently being strongly advocated for use in clinical practice [218, 219], there are no specific recommendations or guidelines for the treatment of arterial health after SCI; however, management should adhere to recommendations for the aforementioned risk factors.

14.5.3.2 Heart

Cardiovascular decline is apparent through a number of deleterious alterations in cardiovascular end organs, some of which occur at a remarkably rapid rate of mere

weeks after the SCI itself [216, 220–222]. Impairments in cardiac structure and function have been extensively reported in the literature in the recent past. Specifically, a number of studies in both rodents and humans have shown a reduction in cardiac size after high thoracic and cervical SCI, whereas those with lower thoracic injuries do not appear to undergo the same changes, despite reduced stroke volume [216, 222–224]. It has recently been demonstrated in the rodent model that high-level SCI (i.e., T3 complete spinal cord transection) results in marked reductions in cardiac size (i.e., end-diastolic/systolic volumes) after only 7 days [224]. These reductions in cardiac dimensions occurred in unison with decreased cardiac contractility as well as with increased relative wall thickness and myocardial fibrotic collagen expression in the left ventricle. Collectively, these changes are key tenants of cardiovascular decline and cardiovascular disease progression and indicate elevated risk for cardiovascular disease [225].

To date, very few interventions have been examined for the mitigation of cardiac decline after SCI. One of the most promising therapies to date involves passive exercise in the early phase after injury [224]. In rodents who started passive exercise only 5 days after injury, all cardiac impairments noted above were normalized to uninjured control levels after 1 month of intervention [224]. Volume unloading (i.e., incapacity to maintain sufficient venous return to the heart) seems to be the principle mechanism by which these cardiac changes occur after high-level SCI. Both rodent and human studies on prolonged bed rest support the idea that maintaining adequate venous flow back to the heart preserves normal cardiac dimensions and function [226–228] Certainly, human trials are needed and ongoing; however, careful attention should be paid to the critical role volume unloading plays on the heart, especially as it appears that early participation in lower-limb exercise after SCI completely abrogates the majority of cardiac-specific decline in this population.

14.5.3.3 Cerebrovasculature

Unfortunately, the end organ of paramount complexity and importance also suffers significant and critical alterations after SCI. Although we know little about changes in brain morphology after SCI, as mentioned earlier, we do know that cognitive function (i.e., memory, attention/processing speed, executive function) is significantly impaired, and stroke risk is 3–4 times greater in this population [229–237]. Both of these conditions are considered to be at least partially vascular in origin, and we are just beginning to understand the extent of changes in cerebrovascular function after SCI [238, 239]. For example, we do know that people with high-level SCI are less able to maintain cerebral perfusion when undergoing an orthostatic challenge [65], and when blood pressure is low, the cerebrovascular reactivity to cognition (i.e., neurovascular coupling, which describes the efficacious matching of blood delivery to cognitive/neuronal activation) is completely abrogated [240]. These cerebrovascular disorders are associated with declined cognitive performance in able-bodied individuals and those with SCI [62, 241]. It appears that low blood pressure is a major contributing factor to impaired cerebrovascular reactivity in those with SCI, which represents a similar causal factor as that which has been elucidated for cardiac decline

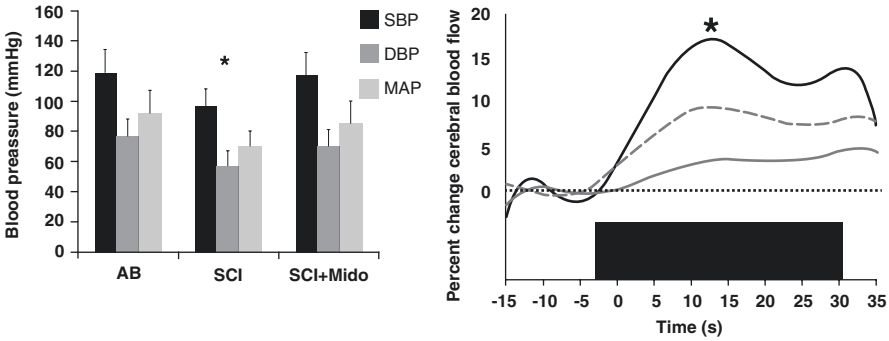


Fig. 14.6 Cerebrovascular reactivity after spinal cord injury. *Left panel*: Blood pressure in able bodied (*AB*), spinal cord injured (*SCI*), and spinal cord injured with normalized blood pressure using midodrine (*SCI + Mido*). *Right panel*: Neurovascular coupling of the posterior cerebral artery in AB (*black line*), SCI (*gray line*), and SCI + Mido (*gray dotted line*). *Thick black bar* denotes 30 s of eyes-open reading, preceded by 15 s of eyes-closed rest. Notice that normalizing blood pressure significantly improved neurovascular coupling. Improved neurovascular coupling as associated with increased executive functioning. *Represents significantly different from AB and SCI + Mido ($P < 0.05$) (Modified from Phillips et al. [62])

(i.e., reduced blood flow/loading) [62, 224, 227]. Please see Fig. 14.6 for detailed description of clinical findings leading to the above contention.

To date, very few studies have examined therapeutic interventions for improving cerebrovascular and cognitive function in those with SCI. Recently, normalizing hypotension by pharmaceutical administration of midodrine hydrochloride (10 mg tablet) was shown to improve cerebrovascular reactivity to cognition, and cognitive function in those with hypotension secondary to SCI [62]. It is important to note, however, that only a small component of cognitive function was measured in this study (i.e., verbal fluency), and although improved, pharmaceutical treatment did not completely normalize cognition as compared to able-bodied controls.

Taken together, systemic arteries, the heart, and cerebrovasculature are impaired in terms of health and function after SCI. These end-organ maladaptations contribute to a variety of clinical consequences such as increased risk of heart attack, stroke, orthostatic intolerance, and cognitive dysfunction. Both cardiac and cerebrovascular functions appear to be detrimentally influenced by reduced hemodynamic perfusion (i.e., low venous return and blood pressure), which can be improved by increasing circulation to the respective organ, such as passive exercise for increasing venous return to the heart and increasing blood pressure to increase blood flow to the brain.

14.6 Managing Cardiovascular Function Following SCI

As cardiovascular dysfunction exhorts such critical effects on morbidity and mortality, a number of strategies have been explored for the prevention and treatment of autonomic/cardiovascular instability after SCI. These have included a number of treatments to be implemented in the acute phase of injury with the goal of limiting

damage to autonomic pathways of the spinal cord as well as interventions designed to treat cardiovascular dysfunction once it has presented after SCI. These topics will be discussed in the following section.

14.6.1 Preclinical Experimental Therapies for Prevention of Cardiovascular Dysfunctions After SCI

As outlined above, cardiovascular dysfunction after SCI is largely the result of disruption of descending autonomic pathways and the subsequent decentralization of the spinal and peripheral sympathetic circuits, resulting in alteration of the autonomic/cardiovascular system. A number of therapeutic approaches have been developed and studied in order to regenerate or preserve descending sympathetic pathways and prevent the resulting cardiovascular dysfunction, although none of these approaches are currently approved for treating patients. These therapeutic approaches have been reviewed recently and will be highlighted below [242].

The preservation of descending supraspinal input using stem cells has been explored in a couple of interesting studies [243, 244]. Early work showed that olfactory ensheathing cells harvested from the animals themselves (and grafted into site of SCI) were able to improve AD (i.e., to reduce the duration of AD episodes) following SCI; however no improvements in resting blood pressure were observed. Unfortunately, when examining the underlying mechanisms, no discernible improvements in CGRP+ sprouting or reduction in injury size occurred making it difficult to ascertain what factors led to the improved autonomic cardiovascular function after SCI. A recent study using brainstem- and spinal cord-derived neuronal stem cell injection into the spinal cord reported a 50 % reduction in AD severity during colorectal distension, as well as a normalization of baseline blood pressure only when using brainstem-derived (but not spinal cord-derived) stem cells [243]. Mechanistically, brainstem-derived neurons led to catecholaminergic and serotonergic neuron axon growth and greater innervation of caudal SPNs, further illustrating the importance of central sympathetic tonic support in the prevention of autonomic cardiovascular impairments after SCI [243].

Another strategy tested to preserve spinal cord pathways after SCI has been the reduction of inflammation. A significant portion of spinal cord damage occurs after the original insult or primary injury due to ischemia, which is considered the secondary injury. The triggering of inflammation leads to the activation of well-established inflammatory processes such as macrophage migration, as well as neutrophil, microglia, cytokine, and matrix metalloprotease influx [245–248]. Together, along with the subsequent free radical generation and lipid peroxidation, neuronal tissue degradation occurs, including destruction of neural and glial cells [249, 250]. The most promising therapy targeting inflammatory processes involves inhibiting leukocyte migration across the blood-brain barrier and, thereby, preventing it from potentially attacking neuronal structures [251–254]. In general this therapy results in roughly a 50 % reduction of AD severity.

A number of studies, using a variety of therapeutic strategies, have specifically targeted the reduction of CGRP+ sprouting in the dorsal horn, which as mentioned is a primary mechanism underlying the development of AD after SCI [39, 45, 48, 251, 255, 256]. The majority of studies have shown that neutralizing the effect of nerve growth factor in the spinal cord after injury leads to improvements (i.e., 35–43 % reduction) in AD [45, 255]. This reduction in AD severity is directly related, albeit through modest coefficients of variation (i.e., r^2 = 0.36–0.64) [39, 48], to reductions in CGRP+ [255], sprouting, and inhibition of TRPV1 somal hypertrophy [35]. These modest coefficients of variation, combined with several studies showing improvements in AD (~50 %) without reductions in CGRP+ sprouting, suggest other major factors are influencing the development of AD after SCI, rather than just afferent sprouting alone [251, 256]. These studies represent preclinical animal models, and if any of these therapies are ever to be widely implemented into clinical practice, stringent human clinical trials are required. Considering the high priority of autonomic issues in those living with SCI, more rapid progress in this area could be achieved by the incorporation of cardiovascular outcome metrics into human trials examining stem cell/anti-inflammatory strategies for motor/sensory issues after SCI, which would provide further insight into the potential benefits of these therapies on autonomic function.

The preservation of descending sympathetic pathways would also provide significant benefit for OH after SCI, and therefore regeneration/anti-inflammation strategies would be suitable for this condition. Due to the difficulty in generating an animal model of OH after SCI, however, there remains limited specific data on therapeutic approaches for OH. In human models, there is a variety of cardiovascular adjustments that may occur after SCI to mitigate or prevent the severity of OH. These include the recovery of spinal sympathetic reflexes, the development of spasticity, increased muscle tone, increased activation of the renin-angiotensin system, maintained cerebral autoregulation and potentially increased tolerance to low cerebral perfusion pressure [5, 65, 166]. Although some of these factors may reduce the severity of OH and/or presyncopal symptoms, OH still is a major clinical problem after SCI, affecting the majority of this population.

14.6.2 Clinical Management of Abnormal Cardiovascular Control Following SCI

Managing episodes of AD and OH is critically important in the clinical setting, due to all of the aforementioned associated clinical outcomes such as heart attack, stroke, cognitive decline, and orthostatic intolerance. A number of interventions have explored pharmacological and non-pharmacological approaches to manage both of these conditions. Clearly, prevention is the first line of defense against episodes of AD and OH after SCI. Non-pharmacological and pharmacological options for management of blood pressure instability after SCI will be presented in this section.

The first component of effective prevention of episodes of AD should include education of patients, caregivers, and family members on proper bladder, bowel, and skin care as triggers originating from these organs (urinary tract infections, constipations, pressure wounds) are among the most common. Second, management of the developed AD event should initially include resolution of the trigger which most commonly will include bladder or bowel evaluation (although this may potentially initially exacerbate AD), but could also include mitigating a variety of noxious or non-noxious stimuli [257]. These immediate interventions should occur while the patient is in a seated position, or with the head elevated, in order to initiate orthostatically mediated declines in blood pressure and reduce the pressor effect of AD. Once an AD event is triggered, and is unresponsive to treatment attempts (blood pressure continued to be elevated above 150 mmHg), it may be required to intervene pharmacologically. Most commonly nifedipine (a short-acting calcium channel blocker), captopril (angiotensin-converting enzyme), or nitropaste (vasodilator) are recommended to mitigate this condition [258]. However, these drugs have been shown to also exacerbate low resting blood pressure [68]. This latter consideration is particularly relevant when considering treatment options for AD in those with SCI as they already suffer from low blood pressure [68, 259]. In an effort to overcome this side effect, the use of prazosin (alpha1 antagonist) has been explored. Recently, prazosin (1 mg oral tablet) effectively reduced AD severity (due to penile vibrostimulation) while exerting no effect on resting blood pressure, suggesting it may be a viable option for treating AD [259]. For detailed guidelines on management of AD, see [68, 257]. It is also possible that botulinum toxin A can reduce the frequency and severity of AD secondary to detrusor muscle overactivity [260, 261]. Typically, 200 units of botulinum toxin A is injected per procedure (diluted in 15 mL saline to 20 U/mL), where it is injected into the detrusor muscle at 20 sites (10U per site), sparing the trigone (see clinical vignette).

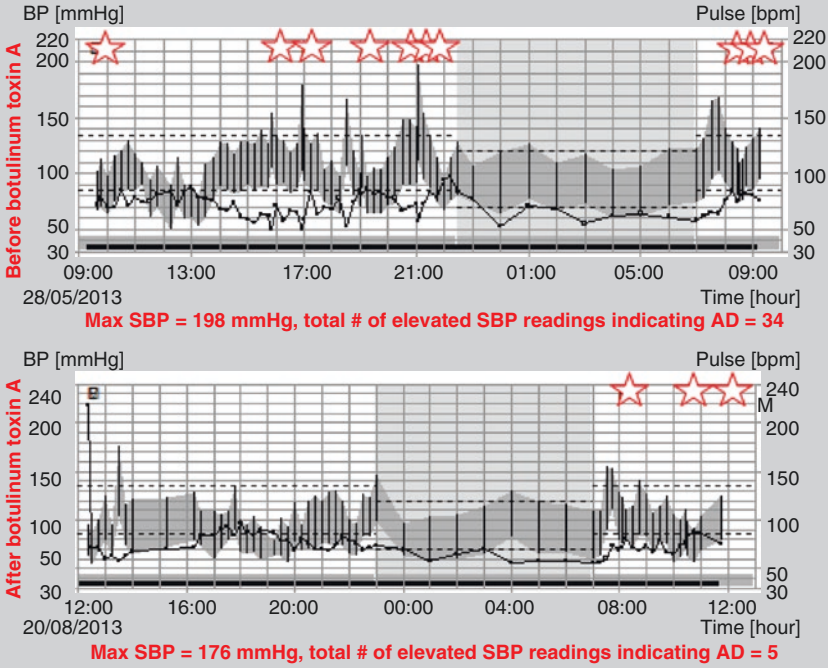
In addition to AD, individuals with SCI can experience episodes of OH on a daily basis, which will require management. The majority of activities of daily living require individuals with SCI to be seated in an upright posture in their wheelchair, which predisposes them to orthostatic instability, as a significant amount of blood accumulates in their abdomen and lower extremities (see above). The initial, most simple, preventative strategies of OH include the following: ensuring appropriate fluid intake; avoiding diuretics, large meals (postprandial hypotension), and heat stress; as well as wearing compression bandages/stockings and potentially engaging in a semi-upright sleeping position (i.e., 10–20° increase) [63, 262–265]. The assumption of a recumbent or semi-recumbent position during daily living can often resolve OH but can significantly influence the patient's quality of life. Pharmacological intervention may be required if these approaches are not effective at reducing OH. Typically these include volume expansion with fludrocortisone [264, 266] and/or increasing vascular tone with alpha1 agonist midodrine hydrochloride [65, 267, 268]. In fact,

maintaining cerebral blood flow using 10 mg of midodrine prevents OH and helps prevent presyncopal symptoms by preserving perfusion of the brainstem where discrete regions responsible for consciousness are located [269]. These approaches are most commonly used in combination, depending on the patient's responsiveness to each intervention, and the severity of autonomic cardiovascular disturbances.

14.7 Summary

Cardiovascular dysfunction in those with SCI is a leading cause of morbidity and mortality in this population and therefore requires careful clinical consideration. Disrupted autonomic pathways result in an unstable cardiovascular system characterized by impairments in blood pressure and blood flow regulation. The majority of those with SCI suffer from daily episodes of blood pressure fluctuation including episodes of AD and OH, resulting in rapid and substantial increases and decreases in blood pressure, respectively. In addition, resting blood pressure is often very low in this population. The clinical community has recently become aware that autonomic issues, such as cardiovascular control, are most frequently ranked by patients with SCI to be of greater priority than regaining motor function. The trajectory of the natural age-related increases in cardiovascular disease progression is increased in those with SCI, resulting in accelerated development of morbid cardiovascular conditions and mortality. Secondary consequences of SCI are only beginning to receive appropriate clinical attention. In the period immediately after high-level SCI, the first major cardiovascular abnormality presents itself in the form of neurogenic shock. After this, other autonomic cardiovascular conditions develop into chronic blood pressure instability. Other contributing factors to cardiovascular disease after SCI include widespread physical inactivity, impaired glycemic control, inflammation, and lipid abnormalities. Together, autonomic dysfunction and these other factors accelerate the decline of end organs, such as the central arteries, heart, and brain blood vessels. The clinical consequences of these conditions extend beyond the obvious mortality risk through heart attack and stroke to also include orthostatic intolerance, cognitive dysfunctions, and impediments to rehabilitation. Although our understanding of blood pressure abnormalities following SCI has certainly been greatly enhanced, we still do not understand the long-term consequences of these conditions and the full extent of their underlying clinical implications. Prevention/mitigation strategies for cardiovascular autonomic function due to SCI are still in their infancy having been explored mainly in animal models, while the majority of cardiovascular disease management guidelines are based off of recommendations developed for non-SCI populations with tenuous relevance.

Clinical Vignette (Patient): 60-Year-Old Male, C6/7, AIS B (34 Years Since Injury)
This SCI patient suffers from severe and frequent autonomic dysreflexia which was significantly impacting activities of daily living and leading to headache, confusion, and frequent sweating. The injection of botulinum toxin A into the detrusor muscle significantly reduced the severity and frequency of AD during urodynamics. Specifically, systolic blood pressure rose more than 70 mmHg during urodynamics in this patient before treatment, which was reduced to only 37 mmHg after botulinum toxin A injection. Furthermore, symptoms of AD reduced substantially, and as shown below the frequency and severity of AD, as assessed by 24 h ambulatory blood pressure monitoring, was drastically reduced. These data suggest that botulinum toxin A may be an effective strategy for treating AD due to detrusor overactivity in those with SCI. Red stars denote identified AD episodes.



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Neuro-Urology in Spinal Cord Injury

15

Jens Wöllner, Jörg Krebs, and Jürgen Pannek

Abstract

Storage and evacuation of urine is regulated by a neural control system that precisely coordinates the reciprocal activity of these two functional phases of the lower urinary tract (LUT) to achieve continence and to ensure a periodic, controlled voiding. This complex control system includes the sympathetic, parasympathetic, and somatic nervous system, with close interaction of cortical, subcortical, spinal cord neural networks and peripheral nerves. Damage to spinal cord structures results in a dysfunction of storage and evacuation, which can lead to incontinence, incomplete bladder drainage, and deterioration of the upper urinary tract. A straightforward categorization of neurogenic lower urinary tract dysfunction (NLUTD) is almost impossible due to the heterogeneity of spinal cord injuries (SCI) in terms of segmental levels of injury and completeness. An individual diagnostic and therapeutic approach is mandatory for successful treatment of NLUTD. This chapter summarizes the physiological and pathophysiological aspects of a SCI and the diagnostic and therapeutic approaches in different phases after the SCI. The diagnostic assessment includes noninvasive procedures like clinical examinations and determination of post-voiding residual volume by ultrasound and invasive procedures such as urodynamic investigation and cystoscopy. The therapeutic interventions contain conservative therapies like drugs and percutaneous electrical stimulation and minimal invasive therapies such as injections of onabotulinumtoxin in the detrusor and sacral neuromodulation. In cases of failure of conservative treatment, invasive treatments among them bladder augmentation and implantation of an artificial sphincter might be necessary. A lifelong surveillance of the neuro-urological function of individuals with SCI is highly recommended to avoid complications and irreversible alterations of the lower urinary tract.

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15.1 Introduction

The integrity of the pelvic organs with non-impaired bladder, bowel, and sexual function is crucial for achieving a high quality of life and is an important issue in the rehabilitation process of individuals with spinal cord injury (SCI). Regaining sexual function and bladder and bowel control were rated with high priority in individuals with SCI [3]. Therefore an examination and treatment of a pelvic organ dysfunction as a consequence of SCI is crucial for a high quality of life in these patients and furthermore, to achieve urinary continence and to maintain the integrity of upper urinary tract function. To reach this goal, regular follow-up examinations are recommended to preserve lower urinary tract function and to avoid a deterioration of renal function. Diagnosis of neurogenic lower urinary tract dysfunction and sexual dysfunction and therapeutic procedures are already initiated during primary rehabilitation. Based on the lesion level, completeness of the injury, the age and general constitution of the patient, and her or his hand dexterity, an individualized treatment concept is set up. A lifelong care with, e.g., annual control exams of these patients is mandatory to avoid long-term complications.

15.2 Physiology and Pathophysiology of the Lower Urinary Tract

The task of the lower urinary tract (LUT) is mainly to store and voluntarily evacuate urine. To fulfill these tasks, a complex cascade of regulation mechanisms at different levels of the central nervous system (CNS) is involved. Supraspinal centers such as the frontal cortex, the pontine micturition center, and the insula are responsible for the voluntary control of micturition [17, 66]. The spinal cord is essential for the transmission of sensory information originating from the LUT to allow for processing of afferent input by supraspinal neural networks. Together with the afferent fibers and the supraspinal centers, descending inhibitory and excitatory efferent fibers from the cortical micturition centers to the lowest sacral segments form a fine-tuned closed loop system to control storage and evacuation of urine.

For the coordinated storage and evacuation of urine, a complex interaction of sympathetic, parasympathetic, and somatic neural networks is required, and the integrity of the connections between cortical, supraspinal centers, and spinal neurons must be preserved. During the storage phase, sympathetic activity is mediated via the hypogastric nerve to inhibit contraction of the detrusor. Furthermore, simultaneous activation of pudendal nerve fibers causes contractions of the internal and external urinary sphincters, thereby achieving continence. The transmission of activity of the pontine micturition center via the spinal cord to suppress detrusor activity is crucial during storage phase (Fig. 15.1a). SCI may destroy these descending inhibitory nerve fibers with the consequence of unsuppressed detrusor overactivity.

In contrast, during the voiding phase, relaxation of the external and internal urethral sphincters is mediated via suppression of the pudendal nerve and inhibition of

the sympathetic activity. The pontine micturition center enables activity of the sacral micturition center to induce a similar detrusor contraction mediated by muscarinic receptors (M2, M3) (Fig. 15.1b).

SCI also affects the efferent and afferent fibers of the LUT, resulting in a disturbed function of it, which is called neurogenic lower urinary tract dysfunction (NLUTD) [54]. Depending on the level and completeness of the lesion, different clinical manifestations (Fig. 15.2) of NLUTD can occur [111]. Neurogenic detrusor overactivity (NDO) is an involuntary contraction of the detrusor muscle which is associated with increasing pressure in the bladder during the storage phase and may result in urinary incontinence. More importantly, in case of a spastic sphincter muscle, elevated intravesical pressures may cause ureter and renal reflux and may have detrimental effects on the integrity of the upper urinary tract. If this condition is over looked and not be treated, it may lead to renal failure [49, 54]. Furthermore, the coordination between detrusor muscle and urethral sphincter can be affected, which can result in detrusor-sphincter dyssynergia (DSD). DSD is a simultaneous contraction of the bladder and urethral sphincter during the voiding phase, which causes a functional obstruction. Consequences are renal damage by either reflux or obstruction of the upper urinary tract. In addition, it can provoke incomplete drainage and elevated post-void residual urine, often leading to recurrent urinary tract infections (UTI).

Lesions of the lumbar or sacral spinal cord are mainly peripheral nerve lesions resulting in an acontractile bladder with insufficient or incomplete drainage. In addition, a flaccid urethral sphincter can cause urinary incontinence. The type of NLUTD is not unambiguously related to a specific lesion level. Furthermore, the type of NLUTD may change within the course of SCI in particular within the first 6 months after SCI. To apply the appropriate conservative or medical therapy, clinical examinations at regular intervals are recommended with shorter intervals within the first year after SCI [54–120].

The schema from Madersbacher (Fig. 15.3) represents an attempt to categorize the different types of NLUTD. Nevertheless, the clinical manifestation and type of the NLUTD are different in each individual patient. Due to the complex interaction between the supraspinal and cortical centers mediating LUT function via the spinal cord, the same lesion level and degree of sensory or motor completeness may not result in the same NLUTD. Differences may be apparent, e.g., in the characteristics of detrusor overactivity (peak vs. plateau), maximum detrusor pressure during storage phase, or overall bladder compliance. The identification of these differences in NLUTD in each individual with SCI is done by a video-urodynamic (VUD) investigation.

Clinical symptoms may be misleading, because even in patients with incomplete lesions and comparable neurological status, symptoms may vary to a large degree from “unaffected, normal” voiding to complete urinary retention. Unfortunately, these symptoms do not correlate with the type and severity of dysfunction, and up to 70 % of the SCI patients presenting with worsening of the pattern of the NLUTD requiring medical treatment do not show additional symptoms [109]. Therefore an exact diagnosis of NLUTD after SCI by video-urodynamic exam is essential.

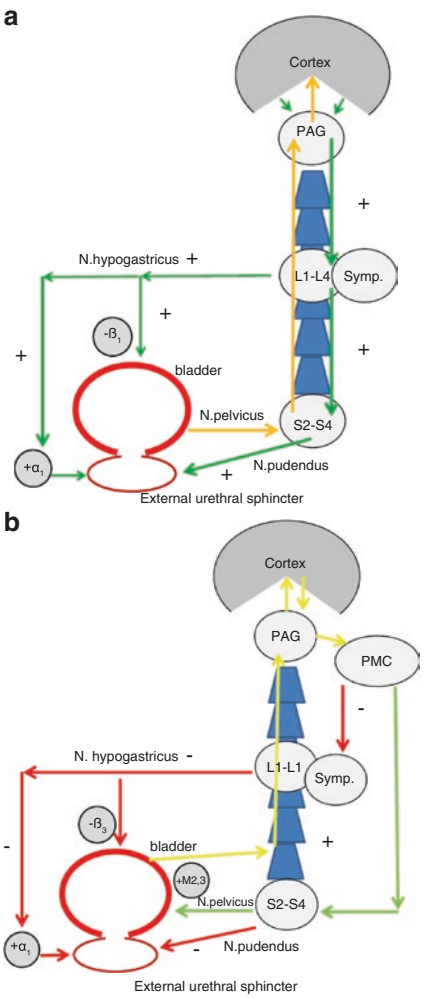

Fig. 15.1 (**a**) Innervation and neural control of the LUT during the storage phase (*Abbreviations*: *N*. nerve, *PAG* periaqueductal gray, *symp*. sympathetic, *L.* lumbar, *S* sacral, $-\beta 3$ beta3-adrenoreceptor inhibition, $+\alpha 1$ −adrenoreceptor 1 activation). (**b**) Neural control of the LUT during the micturition phase (*Abbreviations*: *N.* nerve, *PAG* periaqueductal gray, *symp.* sympathetic, *PMC* pontine micturition center, *L.* lumbar, *S* sacral, *M* muscarinic receptors, $-\beta 3$ beta3-adrenoreceptor inhibition, $+\alpha 1$ − adrenoreceptor 1 activation)

In particular during the first year after trauma, where changes in the neurological status occur, the pattern of the NLUTD can change, and therefore an estimation of the final type and extent of NLUTD is challenging. In the management of NLUTD, the general status, motor impairment, patients' compliance, social circumstance, and patient care after the primary rehabilitation should be taken into account.

Depending on the type of NLUTD, an adequate therapy is essential to maintain a lifelong integrity of the LUT in individuals with SCI. Protection of the upper urinary tract, preservation of renal function, and being continent are crucial for patients' quality of life and participation in daily activities. Therefore, regular and meticulous urologic examinations play a key role in the treatment of patients with chronic SCI.

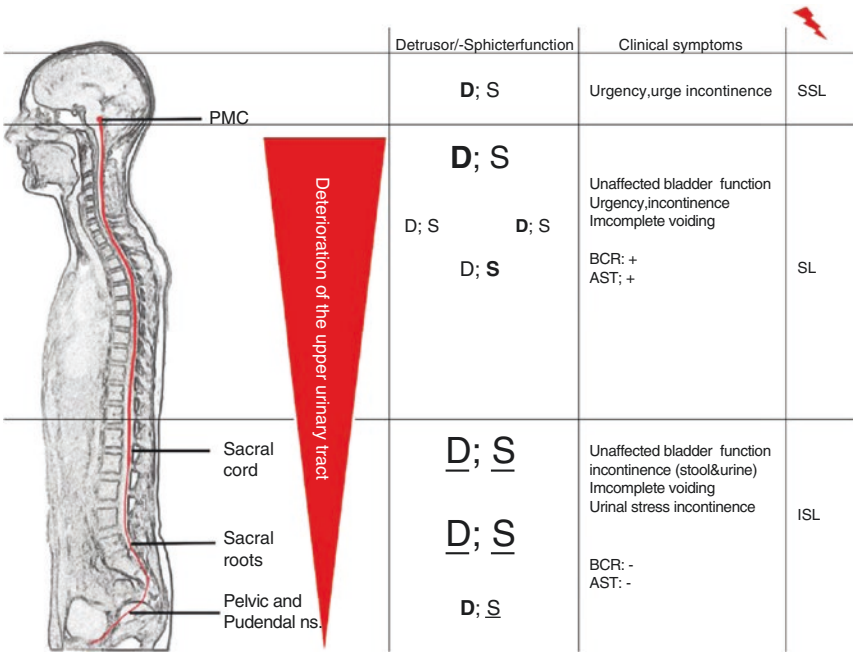

Fig. 15.2 Overview of the pathophysiology of the LUT in SCI (*D* detrusor, *S* sphincter, *SSL* supraspinal lesion, *SL* spinal lesion, *ISL* infraspinal lesion, *BCR* bulbocavernosus reflex, *AST* anal sphincter tone, + positive, – absent). *Underlined letters* stand for "underactive," *normal letters* for "normoactive," and *bold letters* for "overactive." The size of the "D; S" corresponds to the frequency of occurrence

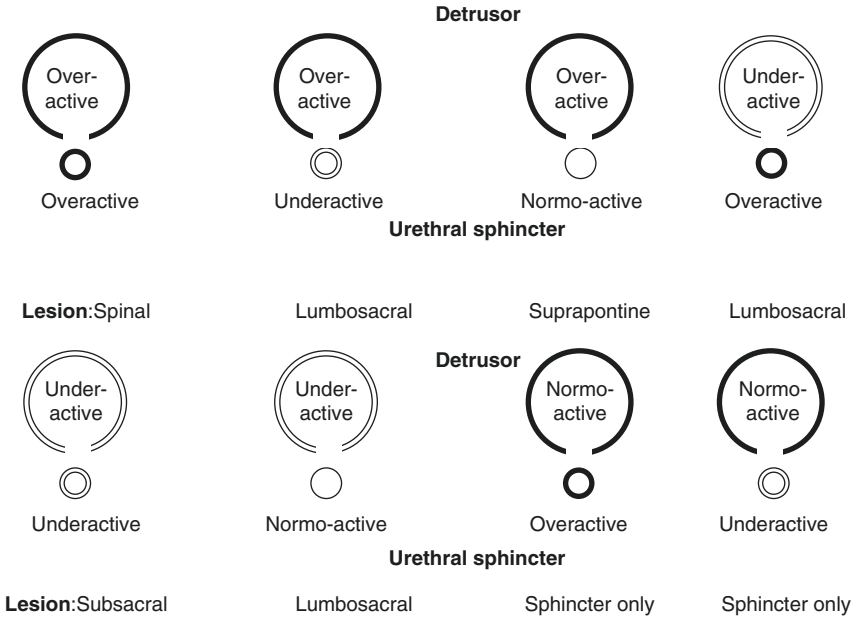

Fig. 15.3 Madersbacher classification of different manifestations of NLUTD

15.3 Diagnostic Procedures

The basic diagnostic approach includes a detailed and complete medical history including the current and previous status of the voiding function (infections, incontinence, hematuria) and surgical interventions at the lower urinary tract, sexual and bowel function, comorbidities, current and previous medication, general health condition, and mental state. Furthermore, the patients' expectations and the aims of the therapy should be discussed.

The physical examination includes palpation of the pelvic region, palpation of the external genital region, prostate exam (men), and testing of sacral reflexes and perianal as well as genital sensations.

Ultrasound of the kidneys and bladder should be a standard procedure to assess renal parenchyma, stone formation, dilatation of the collecting system, and abscess formation. Bladder ultrasound can be used for screening for tumors, stones, and secondary morphologic changes such as a thickened detrusor wall or diverticula. The measurement of detrusor wall thickness represents a useful adjunct tool for the assessment of detrusor function and may evolve to a standard examination in the future [118].

Urine analysis is necessary to indicate UTI. An additional urine culture including the identification of any antibiotic resistance is mandatory in patients with NLUTD, as specific antibiotic treatment is recommended in these patients in order to prevent microbiological resistance [54–120].

Urodynamic investigation is the current "gold standard" to evaluate the LUT function [54–120]. During this investigation, a thin indwelling catheter is used to fill the bladder with saline solution at body temperature with a slow filling speed (<30 ml/min) until the maximum bladder capacity is reached. Simultaneously, the intravesical and the intraabdominal pressures are measured continuously. In addition, the electromyographic activity of the external sphincter muscle is measured via surface electrodes. The procedure of the examination should follow the current guidelines for good urodynamic practices [142]. By using contrast media for bladder filling during the urodynamics together with fluoroscopy (video-urodynamic (VUD) investigation), synchronous, dynamic imaging of the LUT is possible. This procedure allows the detection of secondary changes of the LUT morphology (e.g., bladder stones, diverticula, prostatic influx), vesicoureteral reflux, or detrusor-sphincter/bladder neck dyssynergia. In addition, morphological alterations (e.g., vesicorenal reflux) can be related to functional changes (e.g., detrusor overactivity). The combination of morphologic and functional evaluations is mandatory for treatment stratification and for identification of risk factors for upper urinary tract damage such as low compliance and/or high pressure during the storage phase above 40 cm H_2O [54–120].

Additional examinations such as fluoroscopy of the male urethra, cystoscopy, or other imaging procedures, e.g., transrectal ultrasound, retrograde ureterography, computed tomography (CT), or magnetic resonance imaging (MRI), may be necessary for a thorough diagnosis of unusual clinical presentations. In particular in patients with autonomic dysreflexia, anesthesia may be required for cystoscopy. In

any case, a flexible cystoscope should be used whenever possible to avoid harm to any anatomical structure.

15.3.1 Timing of Diagnostic Procedures During the Acute Phase

During the primary rehabilitation phase, an initial urological evaluation should be established as soon as possible, preferably within the first 2 weeks. After acute care, i.e., after decompression surgery of the spinal cord and stabilization of spine structures, when the patient is in a general condition that allows removal of an indwelling catheter, the bladder management for the first rehabilitation phase needs to be set up. Therefore, a review of the medical history and an ultrasound examination of the lower as well as the upper urinary tract are recommended to exclude any pathological findings on a structural level that may preclude certain treatment options. The initial bladder management regime should be defined based on the results of these evaluations, the general health status of the patient, and associated comorbidities [54].

As a general rule, during the very first days to weeks after SCI – the so-called spinal shock phase – the detrusor is reflexive. Therefore, no risk for detrusor pressure related damage of the upper urinary tract exists. Bladder management procedures in the early phase consist mainly of complete evacuation of the bladder to prevent overdistention and renal damage by obstruction.

After the spinal shock phase, detrusor activity might recur, with the associated risk for incontinence and pressure-related renal damage. Therefore, an initial VUD examination should be performed usually within the first 8 weeks after injury to check for the presence of potential risk factors causing damage to the upper urinary tract.

Depending on the type of NLUTD and the initiated therapy regime, a second urodynamic examination is recommended 8–12 weeks later. This examination is important to evaluate treatment effectiveness if urologic treatment has been established or to detect early signs of a clinically asymptomatic neurogenic detrusor overactivity (NDO).

Depending on the findings of the second VUD, the course of SCI, and the bladder management regime, an additional VUD might be useful at the end of the primary rehabilitation phase at 6 months. In case of unexpected complications or an unfavorable outcome (e.g., recurrent, symptomatic UTIs, new onset of urinary incontinence, increasing post-void residual urine, or autonomic dysreflexia), further examinations are necessary to optimize the bladder management (Fig. 15.4).

15.4 Bladder Management During the Acute Phase

In general, the main focus of NLUTD therapy at any time point after SCI is to protect the integrity of the upper urinary tract namely renal function. Further important aims are achieving continence, avoiding recurrent UTI enabling patients to manage their bladder independently, and adapting the bladder management to the general

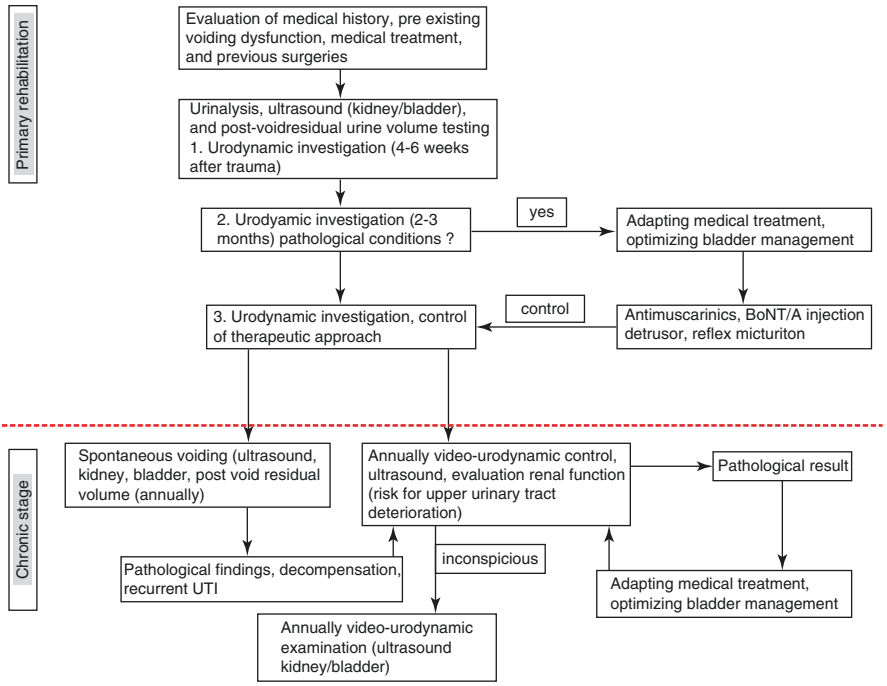

Fig. 15.4 Flowchart of diagnostic procedures in different phases after SCI

condition of the patient. To fulfill these goals, an appropriate bladder management in the acute phase and during the whole primary rehabilitation is crucial.

The primary goal of the bladder management during the acute phase is to ensure a low-pressure urinary drainage without significant residual urine, that is, less than 20 % of the maximum bladder capacity. Initial bladder management immediately after the onset of SCI is commonly an indwelling catheter-either transurethral or suprapubic. To avoid secondary complications, e.g., urethral strictures or recurrent UTI transurethral catheters should be removed and replaced by alternative drainage systems as soon as possible. The intermittent self-catheterization (ISC) is regarded as the optimal bladder evacuation method in cases of insufficient capability to void voluntarily [54–120]. In patients with the inability to perform ISC, either due to comorbidities or due to the extent of motor impairment, assisted catheterization is an alternative. Especially in tetraplegic patients with a lesion level of C4 and above and very limited hand function, ISC is hardly a realistic option. To avoid a permanent suprapubic catheter, the establishment of the reflex voiding with a condom sheet represents an alternative. Patients with motor incomplete lesions (ASIA Impairment Scale (AIS) C and D) may at least partially recover from NLUTD and might regain the ability for spontaneous/voluntary micturition.

The aim of the neuro-urological treatment during primary rehabilitation is to set up and establish procedures for a proper bladder management in each individual patient that reliably protects renal function. Ideally, this treatment should also be convenient, non-invasive, and not time consuming. Due to the probability of neurological recovery during the primary rehabilitation, irreversible surgical interventions should be avoided at this early time point.

Depending on the level and completeness of the lesion, several types of NLUTD occur. Initially, after the onset of SCI, during the so-called spinal shock phase, an acontractile bladder is present. After days to a few weeks, various types of NLUTD may occur, and it has been demonstrated that it is not possible to predict the type of NLUTD. Although in theory, there should be a difference between suprasacral lesions with intact lower motor neurons and lesions of sacral segments with the associated loss of peripheral nerve fibers [29]. Therefore, urodynamic examinations are mandatory for selection of appropriate treatments. An acontractile bladder requires generally no other treatment than evacuation at regular intervals, e.g., by self- or assisted intermittent catheterization (IC). Patients with detrusor overactivity usually need treatment to reduce the elevated detrusor pressure during storage, which will enlarge bladder capacity, lead to continence, and protect renal function. Treatment options may be physical, pharmacological, minimally invasive, or surgical and are discussed in detail in the following paragraphs.

Symptomatic UTI can affect the patients during primary rehabilitation. Especially infections with negative effects on the general health condition may delay the rehabilitation process. In addition, the number of nosocomial infections caused by multi resistant bacteria is constantly increasing [164]. Therefore, meticulous care should be taken to prevent UTI, especially by performing IC under strictly aseptic conditions.

15.4.1 Holistic Rehabilitation Approach

SCI may result in an impairment of motor, sensory, and autonomous functions below the level of lesion. Therefore, SCI does not only lead to NLUTD, but results in limitations of a broad spectrum of activities including mobility and self-care. These functional limitations may represent a barrier for participation in a professional work environment, maintaining social relationships, participating in leisure activities, and being active members of the community. Participation restrictions are highly influenced by environmental factors, e.g. accessibility and availability of adaptive equipment and support [128]. Thus, SCI rehabilitation should comprise all the mentioned aspects. The International Classification of Functioning, Disability and Health (ICF) serves as a comprehensive and universally accepted framework to classify and describe functioning, disability, and health in people with SCI [127]. The ICF comprises four components: body functions, body structures, activities and participation, and environmental factors [128]. Because dedicated SCI care achieves better outcomes than general, nonspecialized care [37, 148], integrative and comprehensive care involving multidisciplinary teams under the supervision of a

physiatrist or a specialist in physical medicine and rehabilitation should be established. The bladder management for an individual with SCI must not be chosen based on the urodynamic data alone, but the aforementioned biopsychosocial factors have to be included in every decision. For example, assisted IC may not be suitable for a tetraplegic male patient returning to work, thus reflex voiding is a more feasible alternative. In patients with brain injuries, antimuscarinic medication may aggravate cognitive dys function; thus onabotulinumtoxin injections may be more appropriate. Surgical interventions during the initial rehabilitation may delay the primary rehabilitation process and should therefore be postponed if other alternatives can still be applied.

15.5 Bladder Management in the Chronic Phase

The ultimate goal of a urologic long-term management of NLUTD is the protection of renal function. An elevated detrusor pressure during storage phase, either due to low bladder compliance or because of detrusor overactivity combined with DSD, is the major risk factor for degradation of renal function [49]. Therefore, the primary goal of the bladder management in these patients is to keep the detrusor pressure low during urine storage and emptying of the bladder [122]. In addition, prevention of secondary morphologic alterations of the lower urinary tract, voluntary bladder emptying at physiologic intervals, continence, and the best possible preservation of quality of life are other important goals of NLUTD treatment. Even in chronic patients, the type of NLUTD is likely to change over time, and clinical symptoms may not reflect the presence of risk factors [109]. As a consequence, urodynamic assessment is mandatory for treatment adaption and risk assessment. A treatment should never be initiated or adapted exclusively only on the basis of clinical symptoms.

A clear recommendation for a cutoff value of the storage pressure that effectively prevents renal damage cannot be easily given. McGuire and coworkers demonstrated that patients with a detrusor leak point pressure less than 40 cm H_2O had a lower risk for upper tract damage compared to patients with a detrusor leak point pressure above 40 cm H_2O [100]. More recently, a storage pressure of less than 30 cm H_2O seems to be most beneficial for the protection of renal function [101]. Besides elevated storage pressure, urinary tract infections and their associated complications are the most significant causes for degradation of renal integrity [152].

Today, detrusor relaxation along with IC is recommended as the standard first-line treatment in patients with neurogenic detrusor overactivity [54–120]. Several methods for detrusor relaxation exist including drug treatment, onabotulinumtoxin injections in the detrusor, and surgical interventions. If the storage pressure can be kept in a physiological range, protection of renal function and in many cases continence can be achieved. In a substantial percentage of patients, however, IC cannot be established, mostly due to the lack of manual dexterity (e.g., in tetraplegic patients) or substantial comorbidities. To avoid indwelling catheters, lowering the outlet obstruction is regarded as a second-line treatment option. By establishing reflex voiding with a reduced outlet resistance, less detrusor force is required,

leading to more effective emptying of the bladder. As a result, fewer UTIs occur, upper urinary tract function is preserved, and – if present – episodes of autonomic dysreflexia are reduced [123]. The disadvantage of this method of bladder management is the urinary stress incontinence, which demands an external urine collecting device, normally a condom catheter, and restricts this treatment strategy usually to male patients.

In selected patients with complete SCI, deafferentation combined with the implantation of an anterior root stimulator can reestablish the capability of urine storage and allow for a user-initiated voiding.

15.6 Treatment of NLUTD

15.6.1 Conservative Treatments

15.6.1.1 Temporary Peripheral Electrical Stimulation

Techniques based on electrical stimulation have not been thoroughly assessed in SCI patients. No comparative studies evaluating the influence of stimulation technique (duration, frequency, impulse width), stimulation site (penile nerve, pudendal, sacral, suprapubic, tibial nerve), and application technique (surface electrodes, rectal/vaginal plugs, needle electrodes) have been performed yet. In acute settings, it has been shown that continuous and conditional stimulation can significantly suppress detrusor overactivity resulting in a higher functional bladder capacity [68] and facilitate voiding. The only long-term study using urodynamic assessments and a follow-up period of 2 years demonstrated long-lasting significant and clinically relevant improvements of the bladder capacity (mean increase of 117.7 ml immediately after stimulation and of 101.6 ml 2 years after the treatment). Post-void residual urine decreased by a mean of 81.9 ml immediately after completion of the 3-month treatment and by a mean of 76.9 ml 2 years after the treatment. Intravesical pressure at maximum flow significantly decreased in 68 % of the study participants. The results were accomplished with 30 transcutaneous stimulation sessions of 15 min duration, using pulsed sinusoidal waveforms (50 Hz) with a pulse duration of 200 ms, pulse pause interval of 1000 ms, and a current intensity of 15–20 mA [131]. Therefore, electrical stimulation, temporary or permanent, definitely holds promise for a better rehabilitation of the lower urinary tract in the future [99]. However, the ideal parameter set and patient group (e.g. only incomplete SCI) still have to be identified.

15.6.1.2 Intermittent Catheterization

In patients with significant residual urine or chronic urinary retention, either due to the NLUTD itself or due to treatment of detrusor overactivity, IC is the treatment of choice [54–120]. IC can be performed either by the patient or by a caregiver, if ISC is not possible due to impairments of the upper extremities, comorbidities or lack of compliance. Whenever possible, ISC should be established. In general, IC is well tolerated. As sterile IC is too time-consuming and expensive to be used as a routine

procedure in daily life, the aseptic or non-touch technique is the method of choice, although no high-level evidence exists that it is associated with a fewer complication rate compared to clean catheterization [129]. The use of hydrophilic catheters is associated with fewer complications, especially UTI in male patients [159]. IC frequency should be individually tailored, aiming at catheterization volumes between 300 and 500 ml, continence, and avoidance of autonomic dysreflexia and/or urgency.

The most frequent complication of IC is UTI. As, however, the different studies evaluating UTI differ in definition criteria, it is difficult to estimate incidence and prevalence of this complication [161]. The avoidance of bladder overdistention by performing IC at regular intervals contributes to the prevention of UTI [160]. Besides UTI, urethral strictures are a common complication in men performing IC. The incidence of urethral strictures increases with a longer follow-up with most events occurring after 5 years of IC [124]. In a recent study from Krebs et al., the long-term (median follow-up 5.9 years) occurrence rate of urethral strictures was 25 % in men using IC ($n=415$), which was significantly higher than in men using other bladder evacuation methods ($n=629$). There was no significant effect of tetraplegia or catheter type on the stricture occurrence rate. Approximately one-third of the men suffering from urethral strictures underwent internal urethrotomies [84]. A history of indwelling catheters or urethral lesions is correlated with a higher incidence of urethral strictures in men performing IC [56].

15.6.1.3 Indwelling Catheters

Despite the mentioned risks of IC, it is regarded as the gold standard for bladder evacuation in SCI patients not being able to voluntarily void effectively. Indwelling catheters bare substantial long-term risks such as vesicoureteral reflux, urethral incompetence and leakage, hydronephrosis, severe autonomic dysreflexia, bladder calculi, labial erosion, hypospadias, and carcinoma of the bladder [10]. The risk for septicemia and death was elevated in persons with indwelling catheters [138]. Comparing the long-term complications of suprapubic (SPC) and transurethral (TC) indwelling catheters in SCI patients, no significant differences in complication rates were detected regarding renal function, bladder stones, UTI, and bladder cancer [72]. The risk for bladder stones is about 25 %, whereas the risk for stone recurrence is elevated in patients with TC compared to those with SPC [8]. In TC, urethral and scrotal complication rates were higher, whereas morbidity related to SPC insertion was higher. If SPC are used, the routine use of anticholinergic medication and clamping of the catheter does not seem to be necessary to preserve detrusor compliance and renal function [116].

15.6.2 Pharmacological Treatment

15.6.2.1 Treatment of Detrusor Overactivity

NLUTD affects the majority of patients with SCI. The main concern in these patients is renal damage as a result of high detrusor storage and voiding pressures

[49] which used to be the most common cause of mortality in SCI [136]. High detrusor pressures result from detrusor overactivity or low bladder compliance, often combined with DSD [25]. Antimuscarinic drugs have therefore become the first-line treatment for alleviating NDO [54–120]. The control of storage and voiding detrusor pressures has resulted in lower mortality rates from urological causes in SCI patients [44]. The efficacy and safety of antimuscarinic drugs, such as oxybutynin, trospium chloride, tolterodine, and propiverine, for the long-term treatment of NDO is well established [54–120]. The antimuscarinic treatment of NDO in SCI patients lasts commonly lifelong, and thus compliance with therapy is an important issue. Unfortunately, SCI patients tend to require higher doses of antimuscarinic drugs than those with idiopathic detrusor overactivity, which in turn may lead to a higher number or more severe adverse events [74] and consequently to abortion of treatment [9, 74]. There is no antimuscarinic drug which has been clearly proven to be superior to others in regard to efficacy-side effect ratio; thus individual testing is mandatory [54]. As protection of the upper urinary tract is the main goal of antimuscarinic treatment, lowering detrusor pressures during the storage phase is essential. Evaluation of treatment efficacy therefore has to be based on urodynamic testing instead of symptoms alone [61]. Until today, only few studies are available on the outcome of antimuscarinic treatments of NDO based on urodynamic assessments in patients with SCI. As all studies differ significantly regarding inclusion and exclusion criteria and duration of treatment, merely head-to-head comparisons can reliably compare the efficacy and tolerability of different antimuscarinic drugs. Significant reduction of detrusor overactivity in patients with SCI has been demonstrated for the traditional antimuscarinic drugs, such as oxybutynin, trospium chloride, propiverine, and tolterodine [41, 97]. More recently, the effectiveness of solifenacin has been proven in SCI patients as well [79], whereas no data on darifenacin or fesoterodine are available.

As persons with NDO due to SCI may need high-dose antimuscarinic treatment, it is important to know that high-dose treatment, either as a combination of different drugs or by increasing the dose of a single substance, can increase the efficacy without significantly increasing the side effects [2, 67].

Regarding side effects, dry mouth represents consistently the most common complaint; also gastrointestinal adverse events were frequently reported. Other possible, but less frequent, side effects are blurred vision and cardiac adverse events, particularly the increase of heart rate and prolongation of the QT interval. However, there is no evidence that the currently used antimuscarinics increase the risk of cardiac adverse events in general [74].

CNS adverse events, especially cognitive impairment, are of particular concern. Until today, however, the incidence of CNS adverse events described in clinical studies is similar to placebo [74]. The mentioned network meta-analysis by Kessler et al. about adverse events of antimuscarinic drugs (though not specifically performed in SCI patients) came to the conclusion that the side effects of most antimuscarinic drugs available do not differ significantly if applied in the recommended dosage. Only oxybutynin immediate release in a dosage above 10 mg/day seemed to lead to more side effects [74].

Mirabegron, a beta-3-agonist, has recently been introduced for the treatment of non-neurogenic overactive bladder. In this patient cohort, based on the limited number of studies currently available, it seems to be a reasonable alternative to antimuscarinic drugs [22]. However, there is no published experience in patients with SCI, and the drug is currently not licensed for treatment of NDO.

In summary, the best antimuscarinic drug has to be determined in each individual patient, based on its tolerability and efficacy obtained by urodynamic assessment. Frequently, several modifications of both the type and the dosage of the drug are necessary.

15.6.2.2 Treatment of Detrusor Underactivity

Currently, no drug with proven efficacy for the treatment of detrusor underactivity exists. It was demonstrated in a cohort of SCI patients with different levels of lesion (cervical, thoracic, and lumbar) that parasympathomimetic drugs do not lead to an improvement of residual urine and/or voiding dysfunction [90]. As this has been proven for other etiologies of detrusor underactivity as well [7], these drugs should not be considered as a treatment option.

15.6.2.3 Infravesical Obstruction

Although urodynamic testing demonstrated a significant reduction of maximum urethral closure pressure, unselective (phenoxybenzamine) and selective (tamsulosin, terazosin) alpha-blockers have only a limited clinical effect on functional bladder obstruction, resulting in a reduction of residual urine and a decrease in maximum detrusor pressure during voiding [1, 59, 93]. Therefore, their use in the treatment of infravesical obstruction has to be individually assessed, as clinical efficacy may vary considerably. However, these drugs may be useful for the treatment of autonomic dysreflexia, especially phenoxybenzamine [59].

15.6.3 Minimal Invasive Treatments

15.6.3.1 Onabotulinumtoxin for the Treatment of Detrusor Overactivity

If the first-line therapy of detrusor overactivity with antimuscarinics is not effective or intolerable due to side effects, the injection of onabotulinumtoxin in the detrusor muscle can increase the bladder capacity and reduce the elevated detrusor pressure [133]. The use of onabotulinumtoxin for treating neurogenic detrusor overactivity was first published in 2000 [143]. The injection caused a significant improvement in bladder capacity and reduced the elevated detrusor pressure. Since this time, intradetrusor injections of onabotulinumtoxin have become a widely used and well-accepted therapy for neurogenic detrusor overactivity. Since 2012, onabotulinumtoxin became licensed for the treatment of neurogenic detrusor overactivity and is currently licensed in the majority of countries worldwide today. Several different products of onabotulinumtoxin are available, in which units of toxin are not comparable to each other. The exact mechanism of action is not yet completely understood, but a direct

efferent effect with inhibition of the presynaptic acetylcholine release is assumed. Furthermore, effects on a variety of different receptors as well as on the afferent nerve fibers are discussed [4]. Depending on the amount of sensitivity preserved, the injection can be performed under local anesthesia. In patients with unaffected sensitivity or risk for autonomic dysreflexia, the procedure should be performed in general anesthesia. Although for neurogenic detrusor overactivity, 200 IU of onabotulinumtoxin is licensed, the dosages used range between 100 and 300 IU, with 300 IU being the most frequently reported dosage for SCI patients performing IC [140]. The effect lasts for a median period between 6 and 12 months; after this period reinjection is necessary [133]. Although a loss of efficacy in up to 25 % of patients during long-term use is reported in single-case series [114], according to current reviews, repeated injections are possible, with no decrease of efficacy [94]. Urinary tract infections in 57–56 %, bleeding in 2–21 %, and urinary retention in 12–42 % are the most frequent side effects, whereas muscle weakness has been reported only very rarely in patients receiving Botox®, and in about 6 % of patients treated with Dysport®, which is not licensed for NDO treatment [94]. Whether antibody formation plays a role as a possible reason for loss of effectiveness still needs to be clarified [94].

In summary, the treatment of neurogenic detrusor overactivity with intradetrusor onabotulinumtoxin injections is a minimally invasive, safe, and effective treatment. Repeated injections are possible.

15.6.3.2 Sacral Neuromodulation

Sacral neuromodulation (SNM) is a minimally invasive approach for the treatment of LUT dysfunction. SNM consists of a two-stage procedure. In the first phase, electrodes are implanted in the S3 or S4 sacral foramina, and a test stimulation phase is initiated. If SNM with temporary electrodes has been successfully applied, impulse generators for permanent neuromodulation are implanted in a second step; otherwise, the electrodes are explanted. Additional interventions to exchange the impulse generators due to a loss of battery charge are required every 4–8 years, depending on stimulation parameters and energy consumption in the individual patient. Currently, no prognostic factors for the success of SNM exist. Thus, a test phase is inevitable.

The mechanism of action has not been completely identified, but a central modulation of afferent and efferent signals in the spinal cord and supraspinal areas seems to play a crucial role [43]. The central modulation is thought to be responsible for the beneficial effects of SNM in both chronic urinary retention and detrusor overactivity, as in both an altered afferent neuronal input seems to be involved in the pathophysiology. SNM is a well-established treatment option for patients with idiopathic LUTS. A systematic review from 2010, however, came to the conclusion that the number of investigated patients with SNM for the treatment of NLUTD was low with high between-study heterogeneity and that there was a lack of randomized, controlled trials [73]. Therefore, SNM should not be used in SCI patients outside clinical studies. In the meantime, some well-documented retrospective case series exist. In a study presenting data from 24 patients with NLUTD due to incomplete SCI, 13 with chronic retention, 11 with

neurogenic NDO, 5 of the 13 patients with chronic retention voided without relevant residual urine and did not require IC anymore. In patients with NDO combined with DSD, neither objective nor subjective SNM success was observed, whereas in patients with pure NDO, a significant decrease in incontinence and a normalization of urodynamic parameters could be observed [95]. In a retrospective case series with 62 patients suffering from NLUTD (majority multiple sclerosis or incomplete SCI (13 patients each), remaining patients with various neurologic disorders), it was shown that SNM also leads to a significant improvement not only of symptoms but also of urodynamic parameters including improvement of DSD in 8 out of 9 patients [27].

Due to the hypothetical mode of action, SNM seems not be effective in complete SCI, as a central modulation is not possible in these patients [144]. In conclusion, SNM should be considered in incomplete SCI patients with NDO or chronic retention, if alternative treatments fail. SNM seems to be effective in both forms of NLUTD present in SCI patients.

15.6.3.3 Minimal Invasive Treatment of Stress Urinary Incontinence

The artificial urinary sphincter is regarded as the treatment of choice for stress urinary incontinence in patients with SCI. However, despite significant success, the complication rates and the invasiveness of the surgical approach stimulated the search for less invasive techniques. The technique, its efficacy, and complication rates are described in detail further below (see paragraph on surgical interventions).

Recently, several minimally invasive treatment options for stress urinary incontinence have been developed. A variety of different bulking agents have been used. Teflon and carbon-coated beads migrate [113]; collagen demonstrated only moderate short-term success and disappointing long-term results [50]. Tension-free tapes are a possible treatment option mainly in females and rarely in male patients, but the clinical experience in patients with SCI is still limited. The published results for alloplastic transobturator suburethral tapes (TOT) in women with SCI are disappointing [117], whereas the short-term results for transvaginal suburethral tapes seem to be more promising [62]. However, experience with both procedures is limited, and especially in the transvaginal suburethral tapes group, the procedure carries the risk of overcorrection by applying too much tension, which may lead to urethral erosion. Therefore, long-term observations are urgently required before these techniques are routinely used. In men, merely two studies exist with small sample sizes.

In summary, the success rate (improvement and cure) is limited to 65 %, and significant complications such as erosion/migration, device infection or failure, implantation site pain, bladder stone formation, and difficult clean ISC were described [55, 102]. Therefore, the technique should be applied with caution in selected patients only.

Lately, new adjustable minimally invasive balloons (ProACT®, Uromedica Inc., Plymouth, USA) have been introduced in SCI patients as well. Only one study with a limited sample size exists, which is not sufficient to recommend the routine use of

this procedure [102]. Autologous myoblasts and fibroblasts for the treatment of stress incontinence are still at an experimental level [91]. Thus, the artificial sphincter still seems to be the method of choice in patients with neurogenic bladder dysfunction.

15.6.3.4 Minimal Invasive Treatments to Lower Outlet Resistance

Today, detrusor relaxation combined with IC is regarded as standard treatment in patients with NDO due to SCI [109]. However, in a substantial percentage of patients, IC cannot be established, mostly due to lack of manual dexterity. Therefore, lowering the detrusor leak point pressure still is a viable treatment option today, especially in tetraplegic men [123]. As a urine collecting device (condom catheter) is required due to the resulting stress urinary incontinence, these procedures are restricted to male patients. To achieve this goal, external sphincterotomy is regarded as the gold standard today. Long-term follow-up has demonstrated satisfying results in the majority of patients [123]. The indications for external sphincterotomy have been described as hydronephrosis, vesicoureteric reflux, and autonomic dysreflexia or recurrent urinary tract infections due to poor bladder emptying [134]. Today, laser sphincterotomy or incision of the external sphincter with an electric knife in the 12 o'clock position is the most frequently used procedure. The most frequent complications are bleeding, infections, and erectile dysfunction [134]. In long-term follow-up, sphincterotomy failure is not infrequent. Its treatment often consists of either re-sphincterotomy or insertion of a SPC [154]. Re-sphincterotomy rates vary between 32 and 82 % [135, 162]. Furthermore, in long-term follow-up, penile retraction can occur, with subsequent inability to apply a condom catheter.

In patients who are reluctant to undergo irreversible surgery, external urethral stents or onabotulinumtoxin injections in the sphincter provide potentially reversible options for treatment of DSD with success rates comparable to sphincterotomy [28]. Over the recent years, several different stents have been used for the treatment of DSD. Basically, permanent stents with urothelial ingrowth, like the UroLume® (American Medical Systems, Minnetonka, USA), and thermosensitive stents without urothelial ingrowth, like the Memokath® (Pnn Medical, Kvistgaard, Denmark), exist. Thermosensitive stents can easily be removed if necessary. Results of temporary treatments with these stents are favorable [63]. Urothelial ingrowth can be a long-term problem in permanent stents, leading to recurrent endoscopic resections [147, 158]. In addition, removal of these stents can be extremely difficult [158]. Despite encouraging short-term results, the long-term results of Memokath® stents were disappointing. Mehta et al. reported that the overwhelming majority of these stents have to be removed due to encrustation, migration, and unresolved dysreflexia [103]. An average time of 13 months for development of encrustation is described [96]. Therefore, stents are mainly used for evaluation of treatment success. If a temporary stent ensured effective bladder emptying, sphincterotomy can be performed, or a permanent stent can be used [47]. Temporary stents can be used as a long-term solution, but have to be replaced if significant problems occur and are therefore an expensive alternative.

Onabotulinumtoxin injections in the external sphincter are another option for treatment of DSD in patients opting for triggered reflex voiding [125]. However, the results on the outcome of this treatment are contradictory. Whereas one study observed a relevant improvement in comparison to lidocaine injections [34], others were not able to show satisfactory results [86]. In addition, the positive effect is temporary, and repetitive injections are necessary. Thus this technique should be used in carefully selected patients who are not willing to undergo sphincterotomy or stent insertion and who do not complain about repetitive interventions [104].

15.6.4 Surgical Interventions

15.6.4.1 Bladder Augmentation

If conservative or minimally invasive detrusor relaxation fails, augmentation cystoplasty is a frequently used surgical option to obtain adequate bladder capacity and low intravesical pressure. Various augmentation techniques using different materials, most commonly ileum segments, have been described [14]. The reported success rates regarding postoperative urinary continence and patient satisfaction, as well as increased bladder capacity and decreased maximum detrusor storage pressure, are high in patients with NLUTD, with no obvious advantage of one technique over another [16, 53, 58, 75, 130]. The postoperative complications associated with augmentation cystoplasty are the same which may result from any major abdominal surgery including small bowel obstruction. More specifically, formation of urinary tract stones, recurrent urinary tract infections, impaired bowel function, metabolic disturbance, and malignancy are the main inherent long-term complications after augmentation ileocystoplasty [53]

In our own series of 29 SCI patients who underwent bladder augmentation, 20/29 patients (69 %) were continent compared to 2/29 preoperatively. Augmentation cystoplasty resulted in a significant increase in the median bladder capacity (from 240 to 500 ml) and compliance (from 13 to 50 ml/cm H_2O). The median maximum detrusor pressure had decreased significantly from 38 to 15 cm H_2O. Complications were observed in 11/29 (38 %) patients, including paralytic and obstructive ileus, impaired bowel function, bladder stones, dehiscence, metabolic acidosis, and autonomic dysreflexia. Approximately half of the patients affected by complications (6/11) required surgical re-interventions [80].

In summary, protection of renal function, adequate bladder capacity, and low detrusor pressure can be achieved using augmentation ileocystoplasty in patients suffering from refractory NLUTD. The most important caveats in SCI patients are bowel dysfunction, as this complication may aggravate preexisting neurogenic bowel dysfunction. Bowel dysfunction, including malabsorption, diarrhea, flatulence, fecal urgency, and incontinence, has been observed in more than 50 % of patients with NLUTD after augmentation cystoplasty [149]. In addition, as SCI patients undergoing bladder augmentation are often younger than bladder tumor patients, in whom also intestinal segments are incorporated in the lower urinary tract, attention has to be paid to malignancies in the augmented bladder. We start

routine cystoscopic examination of the bladder in asymptomatic patients 3 years after ileocystoplasty [5], based on our experience of short latency periods and the severity of the condition. Metabolic disturbances, such as metabolic acidosis or vitamin B12 depletion, seem to be rare complications of augmentation in SCI patients [150]

In conclusion, augmentation ileocystoplasty represents a valuable surgical option for treatment of low bladder capacity and refractory detrusor overactivity in patients with NLUTD, after conservative and minimal invasive treatment options have failed.

15.6.4.2 Sacral Deafferentation and Sacral Anterior Root Stimulation

Sacral deafferentation and sacral anterior root stimulation by an implantable anterior root stimulator (SDAF/SARS), often referred to as "Brindley procedure," has been developed by G. S. Brindley [24] and D. Sauerwein [141]. The technique has been demonstrated to achieve safe detrusor storage pressures, user-initiated voiding in physiologic intervals, and continence in patients with complete SCI, thus resembling the normal bladder cycle more closely than any other procedure [87, 153]. In addition, positive effects on health-related quality of life [155] and even cost-effectiveness [157] have been demonstrated.

In brief, the technique SDAF/SARS consists of intradural deafferentation of the sacral levels S2 to S5 and implantation of an intradural or extradural anterior root stimulator (Finetech Medical Ltd., Hertfordshire, UK). Resection of the afferent sacral roots leads to detrusor areflexia, whereas stimulation of the efferent roots initiates micturition. As stimulation is initiated by a hand-held control device, micturition is voluntary and catheter-free. In addition, the anterior root stimulator can be used for bowel evacuation in about 80 % of the users.

In our own experience, comprising 137 patients with a mean time between surgery and the most recent follow-up of 14.8 years, the long-term success of SDAF/SARS is remarkable. As a result of decreased detrusor pressure in the storage phase and increased detrusor compliance, SDAF/SARS treatment drastically decreased the number of patients being at risk for upper urinary tract damage by more than 75 %. Mean bladder capacity significantly increased from 272 ml preoperatively to 475 ml at follow-up. Furthermore, the annual UTI rate was significantly decreased by more than 50 %. With renal ultrasound no signs of renal obstruction were detected. At the last follow-up visit, 107 (78.1 %) patients were still using the stimulator [78].

Due to the need of intradural surgery and resecting intact nerves, SDAF/SARS is limited to patients with complete SCI and centers with experience in the procedure. Thus, SDAF/SARS will remain an effective treatment option for refractory NLUTD after failure of conservative and minimally invasive treatment options.

15.6.4.3 Artificial Urinary Sphincter

The most important factor in the treatment of stress urinary incontinence in patients with SCI is the exact diagnosis. If urinary incontinence is not caused by sphincter

insufficiency, but by detrusor overactivity, insertion of an artificial urinary sphincter may well lead to severe upper urinary tract damage. Absence or sufficient suppression of detrusor overactivity is an important prerequisite for the implantation of an artificial sphincter.

The artificial urinary sphincter is regarded as the gold standard for the surgical treatment of stress urinary incontinence in male and female SCI patients. Since its introduction in 1973 [146], it has been continuously improved. In post-prostatectomy incontinence, the bulbar urethra is the preferred cuff implantation site. After SCI, however, patients are mostly wheelchair bound, thus putting their whole body weight on the bulbar urethra. Moreover, fluoroscopy frequently reveals an open bladder neck, especially in patients with infrasacral lesions. Consequently, the prostatic urethra is constantly filled with urine, which may be a possible factor for recurrent infections and prostatic influx in male patients. Therefore, sphincter implantation in patients with SCI is recommended at the bladder neck [11].

Patients with SCI undergoing artificial sphincter implantation seem to be at a higher risk for failure of the implant compared to patients with post-prostatectomy incontinence. In a retrospective comparative study, patients in the neurogenic group had a higher risk of nonmechanical device failure, requirement for reoperation, and poor overall long-term continence rates compared to men with a post-prostatectomy incontinence [106]. After a follow-up of at least 10 years, a continence rate of 75 % in predominantly neurogenic patients was demonstrated, but 48 of 61 patients required at least one revision [45].

In summary, high short-term and long-term continence rates can be achieved by the artificial urinary sphincter in SCI patients, but the complication and revision rates are much higher than in patients post prostatectomy [69]. In patients emptying their bladders by IC, the pump is not needed, because an active opening and closure of the sphincter cuff – the only function the pump is used for – is not necessary in these patients. Using a modified technique, in which a port system was implanted instead of a pump, in 51 SCI patients performing IC, a satisfying long-term outcome (median follow-up 8 years) with an objective continence rate of 70.6 % and a subjective cure rate of 90.2 % was demonstrated. With 35.3 % long-term reoperation rates are lower than in most of the previously reported studies [11].

A flow chart summarizes the therapeutic options (Fig. 15.5)

15.7 Urinary Tract Infection and Prostatitis

UTI are among the most common complications of NLUTD due to SCI. In up to 60 % of SCI patients, symptomatic UTI occur after primary rehabilitation [151]. UTI are the most frequent reason for septicemia in this group of patients and are associated with a significant increase in mortality [12, 40]. Furthermore, symptomatic UTI impair the quality of life of the affected persons [112].

Unfortunately, there is no definition of UTI that is universally accepted. The currently best accepted definition defines UTI in patients with NLUTD as the new onset of sign(s)/symptom(s) accompanied by laboratory findings of a UTI

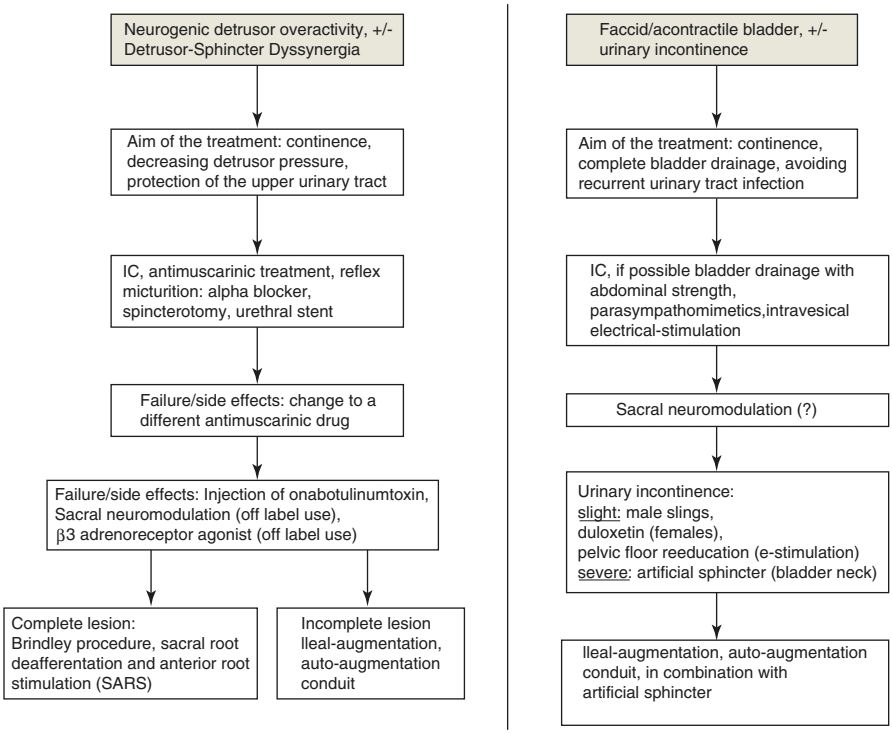

Fig. 15.5 Flowchart of therapeutic procedures of NLUTD

(bacteriuria, leukocyturia, and positive urine culture) [108, 54]. There are no evidence-based cutoff values for the quantification of the laboratory findings.

Individuals with SCI may have other signs and symptoms in addition to or instead of traditional signs and symptoms of a UTI in able-bodied individuals. The most common signs and symptoms suspicious for a UTI in a person with SCI are fever; new onset or increase in incontinence, including leaking around an indwelling catheter; increased spasticity; malaise; lethargy or sense of unease; cloudy urine with increased urine odor; discomfort or pain over the kidney or bladder; dysuria; or autonomic dysreflexia [51, 112]. As UTIs in patients with SCI are related to the underlying NLUTD, UTIs in this group of patients are by definition complicated UTIs.

The diagnosis is based on symptoms, urine culture, and urine analysis. A dipstick test seems to be more useful to exclude than to prove a UTI [35, 65]. In patients with SCI, resistance patterns and the bacterial strains found may differ from those detected in able-bodied persons; microbiologic testing, including evaluation of the resistance pattern, is strongly advised [13]. As mentioned above, signs and symptoms may differ from those in able-bodied persons. To facilitate symptom-based diagnosis, the International Spinal Cord Society (ISCoS) developed a basic data set in which the most common symptoms are listed [51].

15.7.1 Treatment of UTI

As in able-bodied patients, treatment of asymptomatic bacteriuria should not be performed, as this treatment results in significantly more resistant bacterial strains without influencing the risk for symptomatic UTI [42]. As UTIs in SCI patients are complicated UTIs, a single-dose treatment is not appropriate. The duration of treatment is not well defined. In general, a 5–7-day course of oral treatment with a single substance is advised, if feasible [13]. If urogenital organs (kidney, prostate, testicles) are involved, treatment may be prolonged to 14 days [42]. As the causative bacteria are usually not predictable, urine should be taken for a urine culture prior to antibiotic treatment. If it is mandatory to initiate immediate treatment (e.g., in case of fever, septicemia, intolerable symptoms), antibiotic treatment should be chosen based on individual resistance profiles [36]. As SCI often affects young patients, organ-preserving treatment should be performed if possible. In selected patients with epididymo-orchitis, e.g., testicle, preservation is possible even in the case of intrascrotal abscess formation [120].

15.7.2 Recurrent UTI

Recurrent UTI are frequently defined as more than one episode in the last 6 months or more than two episodes in the last 12 months [6]. In persons with SCI, recurrent UTIs may be related to the underlying NLUTD. Therefore, treatment of NLUTD, e.g., detrusor overactivity, residual urine, or resulting secondary problems like bladder stones, is the first step to avoid recurrent UTI [70]. If possible, indwelling catheters should be avoided.

15.7.3 Prevention

If the improvement of bladder function and removal of foreign bodies/stones is not successful, additional UTI prevention strategies should be utilized.

The use of hydrophilic catheters for IC has been demonstrated to be associated with a lower rate of UTI in men, but not in women [26]. Bladder irrigation with various substances, ranging from disinfectants to saline solution, has not been proven effective in the prevention of UTI [156]. However, in patients with ileal pouches, irrigation with tap water had significant impact on bacteriuria [15]. If these results could be replicated in patients with NLUTD, bladder irrigation with tap water may be an alternative technique, especially in patients with indwelling catheters.

The prostate is regarded as a possible source for recurrent UTI in male SCI patients. Recent research could demonstrate that bacteria can be detected in the majority of male SCI patients, but their presence is not related to recurrent UTI [81]. In addition, antibiotic treatment did not lead to bacterial eradication even in SCI patients with bacterial prostatitis [82]. Thus, prevention of recurrent UTI should not comprise treatment of bacteria found in the prostate.

Unfortunately, no evidence-based recommendation for pharmacological prevention of recurrent UTI in SCI patients exists.

The benefit of cranberry juice or cranberry extracts is unclear. Although several small case studies suggested a benefit of cranberry use, the largest randomized controlled trial could not demonstrate a positive effect of cranberry products [88]. As there are huge differences between the different products available (juice, capsules/tablets), especially regarding the concentration of proanthocyanidin, which represents the agent for the antibacterial effect, more studies are needed before a final recommendation can be given. As one of the postulated effects of cranberry products is the reduction of bacterial adhesion to urothelial cells [126], future studies may have to consider also the influence of different bacterial strains on the study results. Other substances frequently used are methenamine hippurate and L-methionine. A Cochrane review came to the conclusion that methenamine hippurate is not effective in individuals with NLUTD [89]. For urine acidification with L-methionine, only a single study with some methodological weaknesses exists, which is not sufficient to support its use [57]. Additionally, the substance may lead to elevated homocysteine blood levels, which is a risk factor for arteriosclerosis [48]. There is one study demonstrating that the bacterial extract OM-89, consisting of immunostimulating components derived from 18 *Escherichia coli* strains, significantly reduces bacteriuria in patients with SCI. However, there was only a nonsignificant trend that the frequency of recurrent UTIs is reduced [60].

Low-dose, long-term, antibiotic prophylaxis is frequently performed. However, this regime does not reduce UTI frequency, but increases bacterial resistance and can therefore not be recommended [42]. Recently, a modified application scheme of antibiotic substances for prophylaxis (weekly cycling oral antibiotics (WOCA)) has been introduced with promising initial results concerning both efficacy and side effects, but the results need to be confirmed in future studies [139].

In summary, as no evidence-based preventive measure for recurrent UTI in patients with SCI exists, the existing methods have to be individually assessed. Initial data imply that additional options may be available in the future. Intravesical inoculation of apathogenic *E. coli* strains has provided positive initial results in small studies which need to be confirmed [30]. In a case series, classical homeopathic treatment provided excellent results which have to be confirmed in a randomized study [119]. In addition, treatment options that were proven to be effective in patients with uncomplicated UTI, e.g., phytotherapy or D-mannose treatment, should be systematically assessed in SCI patients [52, 77]. Finally, new concepts for non-antibiotic antibacterial treatment, as, e.g., bacteriophages, have to be further evaluated in the future [76].

15.8 Sexual Dysfunction

15.8.1 Erectile Dysfunction

The etiology of erectile dysfunction in men with SCI is multifactorial. Although erection is physiologically a result of the parasympathetic innervation of the penis, many other factors, including vascular dysfunctions, medication, depression, or

stress, can contribute to erectile dysfunction. After SCI, psychogenic and reflex erections are possible. A psychogenic erection is usually preserved in patients with an SCI below L3. Reflex erections are generally not possible in patients with injuries from S2 to S4 due to the damage of lower motor neuron axons.

First-line treatment usually consists of oral phosphodiesterase inhibitors, which utilize the nitric oxide-cGMP (cyclic guanosine monophosphate) pathway. This pathway relaxes cavernosal smooth muscle allowing for increased blood flow and in turn creating an erection. Sildenafil, tadalafil, and vardenafil have proven to be comparably efficacious and satisfactory in the treatment of erectile dysfunction in men with SCI [137]. Although some head-to-head comparisons indicate that tadalafil is more effective than sildenafil, especially in patients with lower motor lesions [33], until today there are not enough data available to state that one drug is more effective than the others. Usually, higher dosages are required in men with SCI than in able-bodied patients. Contraindications for phosphodiesterase inhibitors do not differ from those in able-bodied men [145]. However, as men with autonomic dysreflexia due to SCI tend to treat this with nitrates, they have to be specifically counseled not to combine these medications to avoid severe complications [46].

Sildenafil, the most studied drug of the three, has also been shown to be more satisfactory than other treatment options, especially intracorporeal injections and vacuum constriction devices, although intracorporeal injections produced a more rigid erection. However, patients using intracorporeal injections were not satisfied with the route of administration [105]. Intraurethral prostaglandins seem to be less effective than the other mentioned treatment options [18].

Penile implants bare the risk of infections [92] and should therefore be only used in cases where all other treatment options failed and the patients' demands for a therapy are high.

Regarding sensory function, recent studies indicate that a surgical approach connecting the dorsal nerve of the penis to the intact ipsilateral ilioinguinal nerve can restore erogenous penile sensation and improve the quality of sexual health in highly selected patients with absent penile but good groin sensation [110].

15.8.2 Fertility in Men

Male infertility after SCI is characterized by erectile and ejaculatory dysfunction as well as inferior semen quality [21]. The deterioration of semen characteristics appears very early after SCI [31, 98] and mainly affects sperm motility and viability [121]. Long-term cryopreservation results in a significant decrease in sperm motility and viability. Progressive motility and total motility were reduced by 91 % and 84 % to 1 % and 2.5 %, respectively [85]. The ejaculate volume and sperm concentration remain within normal limits, however, in the lower range. Thus, routine long-term cryobanking of semen harvested early after SCI cannot be recommended.

The effects of SCI on semen quality are well described in the literature [21]. The etiology of decreased sperm motility and viability after SCI is still under debate. Although it has been reported that 51 % of men with SCI have at least one hormonal

abnormality [107], there does not seem to be a clear association between hormonal alterations and sperm quality [20]. Spermatogenesis and epididymal function are temperature sensitive, and prolonged sitting in a wheelchair may result in elevated scrotal temperature and consequently in dyspermia [23]. However, ambulatory SCI men also show poor sperm quality [20], and thus elevated scrotal temperature is not likely a relevant contributor to dyspermia after SCI. Balanced accessory gland function is crucial for sperm mobility and viability. In males with SCI, there is evidence of vesicular gland and prostate dysfunction [19, 121]. Furthermore, different biochemical alterations of the seminal fluid have been reported [19]. The seminal fluid of males with SCI may even be toxic for sperm, as it is able to inhibit the motility of sperm from fertile men. In addition, abnormal sperm transport and storage, resulting from autonomic nervous system dysfunction (mainly sympathetic) following SCI, may also contribute to dyspermia [121]. Finally, the altered testicular vascular situation (increased vascular resistance resulting from uninhibited sympathetic activity) may play a role in the development of dyspermia after SCI [83].

As a result of ejaculatory dysfunction, assisted ejaculation is required in more than 90 % of SCI men in order to obtain semen samples [21, 71]. Penile vibratory stimulation is the first-line method for assisted ejaculation, followed by transrectal electrical stimulation for nonresponders [19, 32]. The combined success rate of these two methods ranges between 80 and 90 %.

15.8.3 Fertility in Women

A traumatic SCI does not impair fertility in women. Following a phase of amenorrhea, which occurs in about a third of patients after acute SCI, lasts for about 4 months, and is presumed to be due to a temporary rise in prolactin, reoccurrence of ovulation can be demonstrated, reestablishing the possibility of becoming pregnant for women with SCI [132].

Conclusion

As treatment of NLUTD in patients with SCI is not based on symptoms alone [109], regular controls of upper and lower urinary tract function are mandatory. In SCI patients, this should include video-urodynamic or urodynamic evaluation, bladder ultrasound, and assessment of renal function [54]. Whereas urodynamic examination is standardized, the best method for evaluation of renal function is under debate. Renal ultrasound is useful to detect renal scarring, stones, or dilatation of the collecting system. Regarding blood tests, it is evident that serum creatinine alone is not sufficient, as it is dependent on the muscle mass, which is often reduced in SCI patients. Therefore, serum creatinine levels underestimate the degree of renal damage. The advantage of serum cystatin C levels compared to creatinine is under debate, but most authors regard cystatin C as the superior method in SCI patients [39]. Creatinine clearance is basically a reliable tool, but especially in incontinent patients, urine collection is not always easy.

Renal scintigraphy is the method of choice, as it can assess renal function exactly and separately for each renal unit. However, its availability is limited and it is associated to a radioactive exposure.

Thus, the following strategy can be recommended:

- Within the first 2 weeks after SCI: renal and bladder ultrasound to assess pre-existing morphologic alterations
- After the spinal shock phase (>6 weeks after SCI): video-urodynamics, bladder ultrasound, renal function (serum cystatin C, renal ultrasound)
- 5 months after onset of SCI: urodynamic control
- 9–12 months after injury: (video-)urodynamics, bladder ultrasound, renal function (serum cystatin C, renal ultrasound)

If the assessments mentioned above demonstrate favorable urodynamic results (no risk for renal damage, defined as maximum detrusor pressure < 40 cm H_2O and a detrusor compliance ≥ 20 ml/cm H_2O, normal renal function and normal results on renal ultrasound; [115]), annual controls are scheduled for the first 5 years after SCI. If the controls demonstrate a stable state after 5 years, follow-up intervals can be extended (e.g., every 2 years). If the results are unfavorable (maximum detrusor pressure ≥ 40 cm H_2O or a detrusor compliance < 20 ml/cm H_2O or impaired renal function or abnormal findings on renal ultrasound, [115]), treatment should be initiated, and controls should be performed at shorter intervals until a favorable result has been achieved.

If clinical symptoms, such as recurrent UTI, incontinence, autonomic dysreflexia, decreased bladder capacity, or difficulties in catheterization, occur, a neuro-urological evaluation should be performed as soon as possible. Depending on the symptoms, it should include urodynamic assessment, ultrasound, and cystoscopy, if feasible, and treatment should be initiated.

For treatment of a UTI, urine testing should only be performed if a UTI is suspected due to the presence of clinical symptoms. Regular urinalysis without any clinical symptoms of a UTI may result in a too frequent application of antibiotics and should be discouraged to avoid bacterial resistances.

In patients with indwelling catheters and bladder augmentation, we recommend cystoscopy at regular intervals, initially after 5 years. In augmented bladders other authors suggest a less strict follow-up due to a low incidence of malignancies [64]. In patients with indwelling catheters, the identification of bladder tumors is difficult by cystoscopy alone. Therefore, the best follow-up strategy is still under debate [38, 163].

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Neurogastroenterology in Spinal Cord Dysfunction

16

Gregory M. Holmes, Timothy R. Hudson, and Rosemarie Filart

Abstract

The devastating losses of motor and sensory function are sequelae of traumatic spinal cord injury (SCI) and nontraumatic SCI. Cumulatively, these two categories of SCI are referred to as spinal cord dysfunction. The latter type of SCI has been related to spinal cord injury due to benign or malignant tumor compression, vascular or hemorrhagic injuries, radiation myelopathies, and hereditary and acquired inflammatory or immunologically induced lesions. In this chapter, spinal cord dysfunction will be used interchangeably with SCI when referring to both traumatic and nontraumatic SCI to align with current terminology. It is often less well recognized that individuals frequently present with disorders of the autonomic nervous system which includes gastric, colonic, and anorectal dysfunction. These challenges are widely recognized clinically, yet physicians and caregivers are rarely presented with consistent, evidence-based strategies for successful management of gastrointestinal comorbidities. In the acute stages following traumatic injury, gastrointestinal health is often associated with a more favorable patient outcome during intensive care. Clinically, the most common symptoms relate to diminished gastrointestinal transit, constipation, rectal evacuation difficulties, fecal incontinence, or some combination of these. Additional comorbidities often accompany higher level injuries which may have a major

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negative effect on quality of life. One additional complication of high-level injury at and above the T6 level is autonomic dysreflexia, a potentially life-threatening paroxysmal hypertension induced by noxious stimuli. Gastrointestinal dysfunction can trigger autonomic dysreflexia.

This chapter reviews the anatomy, physiology, function, and neural control of the gastrointestinal tract and the derangements encountered following SCI. The limited preclinical data following experimental SCI is discussed throughout with particular emphasis on identifying both evidence-based therapies and areas for focused research.

16.1 Introduction

The incidence of traumatic spinal cord injury (SCI) is approximately 250,000–500,000 worldwide each year [1]. Inconsistent reporting methods and regional mortality rates preclude a reliable estimate of the current worldwide traumatic SCI population, but it has been conservatively reported at approximately 2.5 million. The incidence of dysfunction following nontraumatic SCI is less well documented but may exceed 100 per 100,000 in certain countries [2].

Based upon extrapolation from percentages in the literature [3], approximately 100,000–300,000 of those individuals with SCI are at risk for developing gastrointestinal dysfunction. The prevalence of gastric, colonic, and anorectal dysfunction after SCI is widely recognized clinically and presents a daily challenge for both caregivers and the overall health status of the individual living with SCI. Gastrointestinal complications are typically responsible for 11 % of hospitalizations in the SCI population [4, 5] and are consistently rated as serious quality of life issues [6]. Furthermore, individuals with SCI often present with life-threatening septicemia, which may occur following bacterial translocation across epithelial barriers, including the gastrointestinal tract [7–9]. Despite the wide-ranging impact to overall quality of life, gastrointestinal symptoms following injury remain largely understudied, and significant knowledge gaps persist regarding the mechanisms leading to postspinal injury gastrointestinal impairments. Limited evidence-based standards of care further complicate the consistency with which therapeutic interventions are applied.

Ultimately, proper gastrointestinal function is critical for the well-being of the individual following SCI [10, 11]. In the acute stages following most injuries, nutrient homeostasis is often associated with a more favorable patient outcome, though the timing and route of nutritional supplementation after SCI remains controversial [12, 13]. Upon progressing from the acute phase of injury, individuals with chronic SCI are commonly offered limited, sometimes invasive, interventions to manage long-term gastrointestinal symptoms.

The principal functions of the gastrointestinal tract center upon the digestion and absorption of nutrients, the maintenance of proper fluid balance, followed by the storage and passage of undigested material. In addition, specialized endocrine cells

within the gastrointestinal epithelium secrete numerous gastrointestinal peptides that serve to regulate digestive reflexes and energy intake. These roles are achieved throughout the neuraxis by a complex interaction of enteric, autonomic, and somatic innervation that is modulated to varying degrees by higher-order regions of the central nervous system. Together, this brain-gut axis is responsible for the homeostatic needs of both the gastrointestinal tract tissues and the organism.

Following the resolution of the spinal shock phase, the level and severity of a spinal cord injury has a profound impact upon the ensuing gastrointestinal dysfunction. Due to the segmental distribution of the spinal neurocircuitry regulating both visceral preganglionic and somatic motoneurons, the degree of disability, morbidity, and mortality following injury tends to be associated with the spinal level at which the injury occurs [14]. In general terms, functional gastrointestinal impairments present as a broad range of symptoms which include delayed gastric emptying, early satiety and the sensation of nausea, bloating, abdominal pain, and diminished propulsive transit along the entire length of the gastrointestinal tract. The reduction in swallowing reflexes and esophageal sphincter tone may also provoke reflux of gastric contents and aspiration pneumonia.

Finally, an injury of the spinal cord at any level will universally affect distal bowel function with constipation, rectal evacuation difficulties, decreased anorectal sensation, and overflow incontinence. These are commonly occurring problems which have a negative effect on the quality of life, reducing social integration and independence. One specific, potentially life-threatening, complication that occurs in some patients is autonomic dysreflexia. The predominant sign of autonomic dysreflexia includes paroxysmal hypertension that stems from an exaggerated sympathetic activation in response to noxious afferent stimuli. Furthermore, autonomic dysreflexia is often accompanied by reflex bradycardia and common signs of autonomic activation such as headache and sweating (Table 16.1). Bowel management

Table 16.1 Common GI causes of autonomic dysreflexia

Potentially, any irritant to the abdominal wall and viscera such as
Ulcer
Cholecystitis
Pancreatitis
Hepatitis
Masses
Gastroenteritis
Hemorrhage
Constipation
Bowel obstruction
Superior mesenteric artery syndrome
Tight clothing or materials over the abdomen
Abdominal wall wound infection
Malfunctioning ostomies, tubes, and drains within the abdominal wall
GI interventional procedures

can trigger autonomic dysreflexia, but this can also be induced by inadequate bowel care, so the balance requires careful stepwise bowel management to minimize the risk of this serious outcome. The need for comprehensive bowel management is further underlined by the increasing life expectancy of individuals with SCI and hence the increasing burdens regarding the management of bowel function.

This chapter reviews the anatomy, physiology, function, and neural control of the entire gastrointestinal tract and the specific derangements encountered following SCI. The limited preclinical data following experimental SCI is discussed throughout with particular emphasis on identifying both evidence-based therapies and areas for focused research.

16.2 Background

16.2.1 Gastrointestinal Anatomy

The gastrointestinal tract of vertebrates is the culmination of a complex and sophisticated evolutionary process [15, 16]. At its most elemental level, the vertebrate alimentary canal consists of an epithelial layer enclosed by an innervated muscle layer and organized along an oral to anal arrangement. The so-called through-gut system of vertebrates, however, is more than a mere tube absorbing and propelling nutrients along a longitudinal gradient. Specifically, the gastrointestinal tissue consists of a laminar organization of five distinct layers, each of which plays a vital role in digestion, absorption, and propulsion (Fig. 16.1).

Regional specialization dominates the entire length of the gastrointestinal tract such that differentiated functions are performed along the proximal-distal path. The

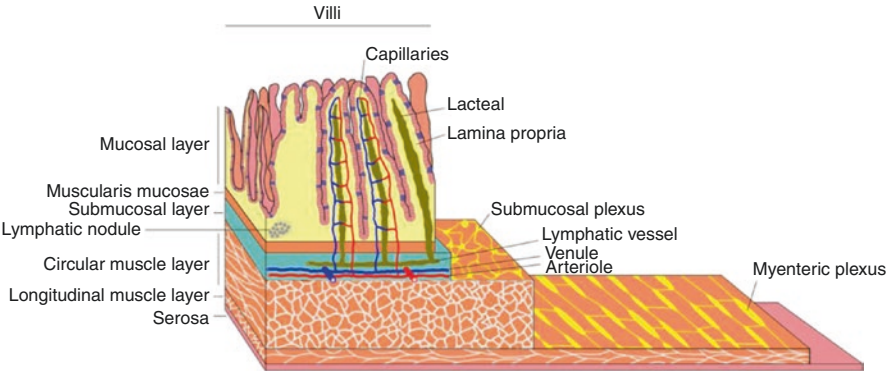

Fig. 16.1 Proceeding along the apical to basolateral direction, gastrointestinal tissue layers consist of mucosa (the tissue in direct contact with the luminal contents), submucosa, circular smooth muscle, longitudinal smooth muscle, and serosa. In addition, the submucosal layer is invested with the submucosal (Meissner's) plexus, whereas the myenteric (Auerbach's) plexus innervates the circular and longitudinal muscle layers. Combined, these plexuses provide the local neural control of the gut and are generally conserved across mammalian species

principal organization of oropharynx, esophagus, stomach, small intestine, and colon is present in monogastric species such as humans and rodents, the primary subjects discussed in this review. The digestive processes of the gastrointestinal tract are augmented by the liver, gall bladder, and pancreas. In non-Western medicine, the spleen is also considered to play an essential accessory role in digestive functions.

16.2.2 Overview of Gastrointestinal Neural Regulation

The principal nutritive functions of the gastrointestinal tract center on the propulsion, digestion, and absorption of nutrients and the maintenance of proper fluid balance. Each is critically dependent upon a hierarchy of enteric, parasympathetic, and sympathetic neural control. In addition, the gastrointestinal tract is the largest endocrine organ in the body, secreting enteric peptides to regulate local gastrointestinal homeostasis as well as regulating organism homeostasis through effects on the brain. The projections and the extent to which each of these complex neural circuits contribute to these processes varies as does the susceptibility to the effects of spinal cord injury.

16.2.2.1 Enteric Innervation

As previously mentioned (Fig. 16.1), the gastrointestinal tract possesses intrinsic innervation in the form of the submucosal and myenteric plexuses that contain the neural circuitry capable of independent reflex function and quasi-autonomous control of the gastrointestinal tract. The extent, and sophistication, of the enteric nervous system has long been evident in the reflexive control that remains even when the gastrointestinal tissues are isolated from extrinsic inputs [17]. The enteric nervous system mediates digestion through localized control over the specialized cells and individual reflex systems for the smooth musculature, secretory glands, and microvasculature of much of the digestive tract (reviewed in [18]). Briefly, functional units of the enteric nervous system are formed by a polysynaptic circuit consisting of sensory neurons, interneurons, and motoneurons, all of which serve in a manner that is similar to many reflexive or integrative neural circuits [19]. For example, sensory neurons (commonly termed intrinsic primary afferent neurons) consist of neurons that respond to either specific chemical cues, mechanical distortion of the mucosa, or distortion of sensory processes embedded within the muscle layers. These afferent neurons terminate onto excitatory or inhibitory interneurons that project in distinct aboral or oral directions. In turn, these interneurons terminate on excitatory or inhibitory motoneurons innervating the smooth musculature. This example illustrates how the enteric nervous system contains the reflex motor programming necessary for propulsive movement as well as retropulsive movement of intestinal contents and segmentation (reviewed in [20]). Of particular relevance to the paced, quasi-autonomous activity of the smooth muscles is the recent interest in the role the interstitial cells of Cajal play in examples of gastrointestinal health and disease [21–23].

Limitations regarding the cross species interpretation of the neurochemical coding of the enteric nervous system have been noted [24, 25]. However, the classical neurotransmitters acetylcholine and serotonin are perhaps the most predominant across species (reviewed in [25, 26]). The gaseous mediator, nitric oxide, is also highly conserved across species (reviewed in [26]). Beyond these neurochemical phenotypes, vasoactive intestinal peptide [27], substance P [28], enkephalins [29], γ-aminobutyric acid (GABA, [30]), and numerous others have also been identified (reviewed in [31]). Evidence is emerging that carbon monoxide and hydrogen sulfide are additional gaseous mediators besides nitric oxide that serve important signaling functions in gastrointestinal physiology [32].

16.2.2.2 Parasympathetic Innervation

Significant parasympathetic innervation of the gastrointestinal tract originates from the brainstem, via the vagus nerve (Fig. 16.2). While vago-vagal reflex circuits modulate digestive processes from the oral cavity to the transverse colon, the level of vagal control diminishes caudally [33–36]. It is generally accepted that vagal input terminates at approximately the second segment (the proximal 2/3) of the transverse colon and the portions of the gastrointestinal tract comprising the distal transverse colon receive parasympathetic input from the sacral spinal cord, via the sacral roots. These parasympathetic fibers distribute to the gastrointestinal tract through the pelvic nerve.

Acetylcholine is the ubiquitous neurotransmitter of the parasympathetic preganglionic neurons and acts through binding to nicotinic receptors [37]. The neurochemical phenotype of the parasympathetic postganglionic neurons is distributed across cholinergic neurotransmission that acts through binding to muscarinic receptors [38] and non-adrenergic, non-cholinergic phenotypes [39–42].

16.2.2.3 Sympathetic Innervation

Preganglionic sympathetic innervation of the gastrointestinal tract originates from the intermediolateral cell column (lateral horn) of the spinal cord between the 5th and 12th spinal thoracic segments (Fig. 16.2). In turn, the sympathetic axons terminate throughout the paravertebral sympathetic chain or form the thoracic splanchnic nerves terminating on postganglionic neurons within either the celiac or superior mesenteric ganglia. The former innervates nearly the entire length of the gastrointestinal tract, from the stomach to the ileum, while the superior mesenteric ganglion projects to the ascending and transverse colon. In addition, sympathetic nerve fibers to the splenic flexure and rectum reside within the 1st through 3rd lumbar segments of the spinal cord. These fibers extend to form the inferior mesenteric plexus and the hypogastric plexus. At the level of the hypogastric plexus, sympathetic fibers are joined by the sacral parasympathetic nerves. Paravertebral sympathetic postganglionic neurons of the chain predominantly innervate the blood vessels of the gastrointestinal tract, while the postganglionic neurons residing in the prevertebral ganglia innervate vasculature and the enteric neurons in both plexuses to influence secretory and motor function (reviewed in [43]).

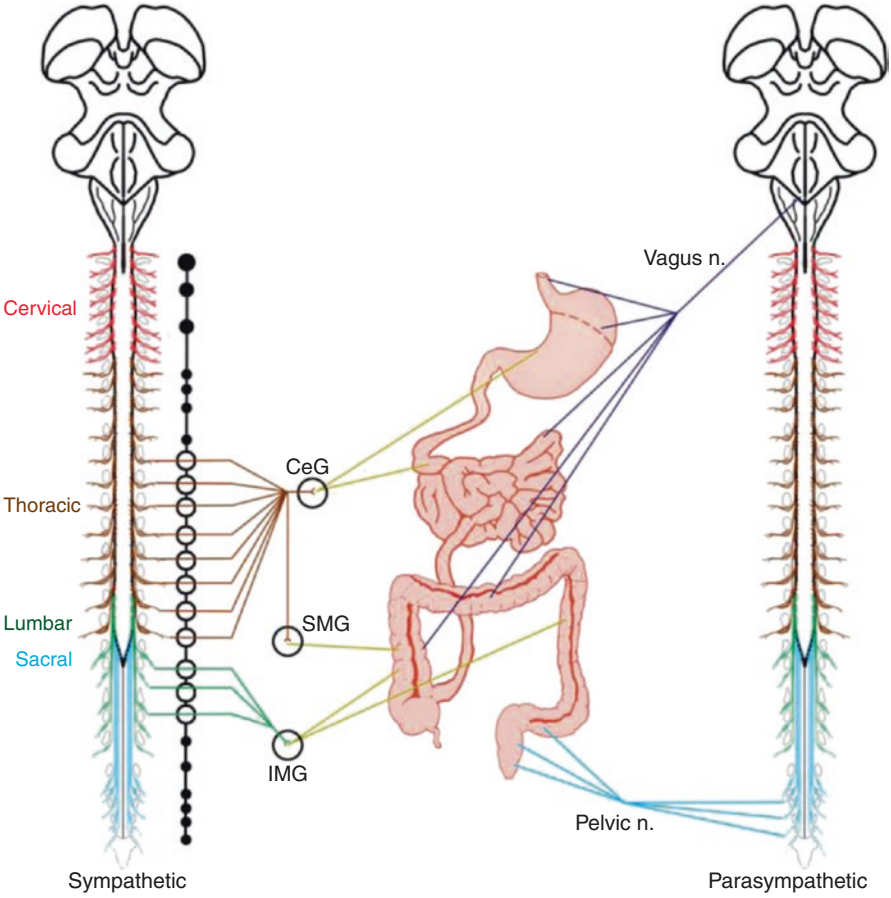

Fig. 16.2 Schematic depiction of the sympathetic and parasympathetic innervation of the gastrointestinal tract. *CeG* celiac ganglion, *SMG* superior mesenteric ganglion, *IMG* inferior mesenteric ganglion

As with the parasympathetic preganglionic neurons, sympathetic preganglionic neurons are cholinergic. The postganglionic neurons, however, are primarily noradrenergic although other neuropeptides and purines are also released. In particular, adenosine 5′-triphosphate (ATP) plays a critical role in the vasoconstriction of submucosal arterioles [44–46].

16.2.2.4 Gastrointestinal Sensory Innervation

The extrinsic sensory innervation of the gastrointestinal tract is a combination of vagal and splanchnic pathways. While vastly outnumbered by the extensive intrinsic sensory neurons of the enteric nervous system, the vagus conveys considerable sensory information in that vagal afferents outnumber efferents by a 10:1 ratio.

Conversely, splanchnic-derived afferents account for less than 10 % of thoracolumbar sensory information.

In order to maintain energy homeostasis of the organism, mechanosensory and chemosensory fibers from the digestive tract are critical for relaying the volume and composition of gastrointestinal contents to the CNS. Briefly, afferent fibers within the vagus nerve innervating the gastrointestinal smooth muscle transduce either the mechanical stimuli generated by distension or contraction, while the chemical coding of pH, nutrient composition, and the postprandial release of neurotransmitters and neuropeptides are conveyed by chemosensitive fibers within the mucosa and submucosa [47]. The transmission, and the ultimate perception, of visceral nociceptive stimuli is generally considered to be relayed through the splanchnic nerves and terminating within the spinal cord [48].

16.2.3 Gastrointestinal Vasculature

The gastrointestinal tract is one of the most highly perfused organ systems in the body (Fig. 16.3). The vascular supply of the oropharynx and the cervical esophagus is through the superior and inferior thyroid arteries. The upper thoracic esophagus is vascularized through esophageal branches of the descending aorta, while the remainder of the gastrointestinal tract is vascularized by the celiac trunk which supplies the distal esophagus, stomach, and the proximal duodenum through three main branches: the left gastric artery, the common hepatic artery, and the splenic artery. The esophagus receives its blood supply from the esophageal artery, which is a branch off of the left gastric artery. The left and right gastric arteries are responsible for the lesser curvature, while the left and right gastroepiploic arteries feed the greater curvature. The duodenum has a "dual" blood supply, arising from both the celiac trunk and the superior mesenteric artery (SMA). Branches that arise from the gastroduodenal artery, a branch of the common hepatic artery, supply the proximal duodenum. These arteries include the supraduodenal arteries, the retroduodenal arteries, the anterior superior pancreaticoduodenal artery, and the posterior superior pancreaticoduodenal artery. The distal duodenum is supplied by the anterior and posterior inferior pancreaticoduodenal arteries, which originate from the SMA. The inferior pancreaticoduodenal arteries form an anastamosis with their superior counterparts, thus creating a collateral circulation between the foregut and midgut.

Approximately 15–18 jejunal and ileal arteries, which arise from the SMA, supply the remainder of the small bowel. These arteries travel within the mesentery, unite, and create arcades, which in turn give rise to vasa recta. In the jejunum, the arcades are simple and short with long vasa recta, while in the ileum, the arcades are complex and display short vasa recta. The SMA provides three additional branches that are responsible for supplying the cecum, ascending colon, and proximal 2/3 of the transverse colon. These branches are the middle colic artery, the right colic artery, and the ileocolic artery. The middle colic artery splits and partially travels

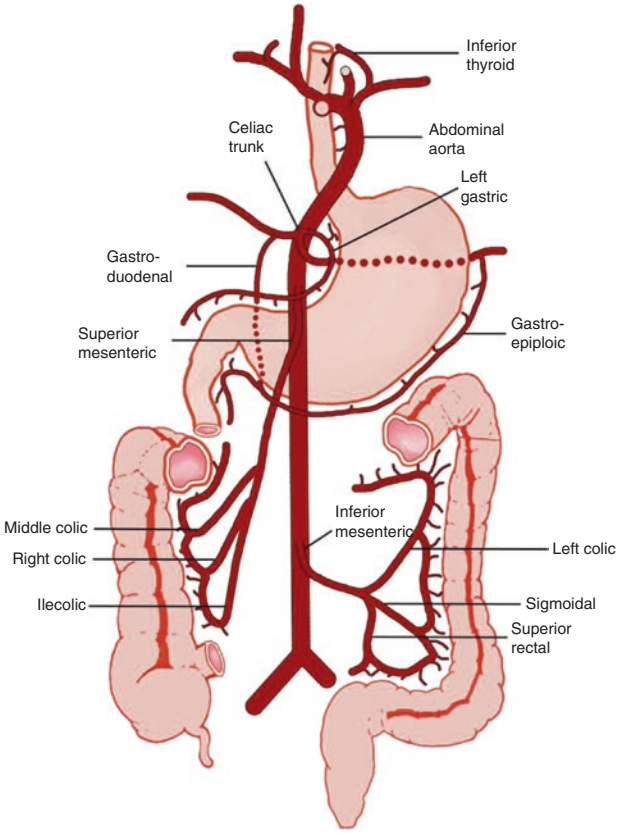

Fig. 16.3 The principal vascular supply of the gastrointestinal tract arises from the celiac and superior and inferior mesenteric arteries. The jejunal and ileal arteries, which comprise much of the mesenteric arcade and the small intestine, were omitted for clarity

along the transverse colon, while the other part anastomoses with the right colic artery along the ascending colon.

Lastly, the inferior mesenteric artery (IMA) is responsible for the hindgut, which extends from the distal 1/3 of the transverse colon to the upper anal canal via three main branches: the left colic artery, the sigmoidal artery, and the superior rectal artery. The left colic artery vascularizes the descending colon and the remaining distal 1/3 of the transverse colon. In doing so, the left colic artery anastomoses with the middle colic artery, creating an arterial connection between the midgut and the hindgut. The anastomosis between the left, middle, and right colic arteries gives rise to the marginal artery (artery of Drummond), which extends the entire length of the transverse colon. Lastly, the sigmoidal artery supplies the sigmoid, while the superior rectal artery provides for the rectum and upper anal canal. The inferior rectal arteries (originating from the internal pudendal artery)

are responsible for supplying the lower anal canal, while the middle rectal arteries (originating from the internal iliac artery) supply the region in between the upper and lower anal canals.

16.3 Upper Gastrointestinal Function in Health and Following SCI

16.3.1 Esophageal Disorders

The incidence of swallowing dysfunction among persons with SCI has been noted from 17 to 43 % in the literature [49, 50]. A common condition is dysphagia which is defined as difficulty in swallowing and may include impairments of moving solids and/or liquids from the oral cavity into the esophagus.

16.3.1.1 Neurophysiology of the Esophagus

Normal swallowing results in the movement of ingested solids and liquids from the oral cavity to the esophagus. Specifically, the task of swallowing involves a complex motor pattern divided into physiologically relevant brainstem effector programs of the oral cavity, pharynx, esophageal body, and esophageal sphincters. The oral phase of swallowing involves voluntary rearward movement of the contents in the oral cavity that triggers subsequent autonomous and coordinated processes. The pharyngeal phase of swallowing includes motor sequences to move ingested items around the larynx, through the pharyngeal esophageal sphincter, then into the esophagus. Equally important autonomous respiratory reflexes of laryngeal elevation and closure, epiglottis folding over the larynx, and adduction of the arytenoids are integrated with esophageal reflexes for proper airway protection [51]. The esophageal phase promotes transient upper esophageal sphincter relaxation and peristalsis in the pharynx and esophagus that propels contents aborally. Ultimately, transient relaxation of the lower esophageal sphincter permits flow into the stomach. Tonic closure of the upper and lower esophageal sphincters prevents retrograde movement of contents unless the specific motor program for reflexive antiperistalsis is evoked in order to propel gastric contents orally as occurs during belching and emesis [52].

Common to the excitatory and inhibitory reflexes necessary for esophageal peristalsis is the dominant role of central pattern-generating neural circuits within the medulla including the nucleus tractus solitarii, nucleus ambiguus, and adjacent reticular neural circuits (reviewed in [52, 53]). Spinal sympathetic control centers for the esophagus have been implicated in reflex functions for vascular, glandular, and sphincter tone [53–55].

Afferent innervation of the esophagus is a combination of spinal projections through the dorsal root ganglia as well as vagal afferent fibers with cell bodies located within the jugular and nodose ganglia (reviewed in [56, 57]). Vagal afferent distribution within the esophagus of laboratory animals is not uniformly distributed but demonstrates greater density proximally [58, 59]. Similar differences in sensory distribution are inferred for humans based upon functional studies [60]. These

limited data suggest that the proximal esophageal mucosa is more sensitive to both mechanical distension and chemical stimulation.

16.3.1.2 Clinical Presentation

Dysphagia symptoms are temporally related to swallowing and may include the inability to voluntarily ingest food, hoarseness, shortness of breath, coughing with swallowing, choking, sensation of food sticking in the esophagus, regurgitation of ingested items into the mouth or nose, sour- or bitter-tasting food and liquids, or chest discomfort [61–63]. Dysphagia following high-level SCI is often accompanied by diminished ability to generate elevated intrathoracic pressures during cough [64], thereby necessitating intensive management of the airway to prevent aspiration pneumonia [65].

16.3.1.3 Clinical Evaluation and Treatment

A bedside swallow evaluation (BSE) is an economical initial evaluation performed at the bedside by a speech pathologist in coordination with a respiratory care practitioner. A positive test is when swallowing dysfunction is identified in any of the phases of swallowing. There are two options for direct visualization using instruments that also will allow for therapeutic interventions: videofluoroscopy swallow study (VFSS) and fiber-optic endoscopic evaluation of swallowing (FEES; [66]). VFSS is a direct visualization of the anatomy and functional test of swallowing. Radiopaque solids and liquids of varying consistencies are visualized using barium and fluoroscopy. Penetration is the movement of solids or liquids entering the larynx, rather than around the larynx. When the movement of solids or liquids flows below the true vocal folds and into the trachea, rather than the normal path of properly flowing down the esophagus, this event is called aspiration. A positive test includes visualization of ingested test materials in the valleculae, pyriform sinus, or larynx or dysfunctional laryngeal elevation or epiglottic closure or inversion. Using a flexible fiber-optic laryngoscope, FEES involves the direct examination of the function of swallowing using trials of varying consistencies of food and liquids. From either VFSS or FEES, therapeutic interventions with "dietary or behavioral" adjustments can be determined. It should be noted that diagnoses of dysphagia in cervical spinal cord-injured population have identified potential confounds. These include causal relationships of dysphagia during artificial ventilation techniques (including tracheotomy) and anterior vs. posterior approaches during spinal stabilization [50, 62, 63]. Treatment of swallowing disorders follows current standard practice for the underlying etiology, and neuromodulatory strategies that promote neural plasticity in combination with standard swallowing rehabilitation practice are research techniques with potential clinical application.

16.3.1.4 Gastroesophageal Reflux

Gastroesophageal reflux disease is the reflux of gastric contents into the esophagus [67]. Normal function is dependent upon the lower esophageal sphincter (LES) and crural diaphragm acting in concert to form a barrier preventing reverse movement of gastric contents into the esophagus. Despite inconclusive evidence of lower

esophageal sphincter dysfunction [68, 69], other reports suggest diminished lower esophageal sphincter tone following SCI. Later evidence in spinal cord-injured subjects demonstrated endoscopic and histological evidence of esophagitis as well as diminished esophageal contractility [70].

The incidence of gastroesophageal reflux disease (GERD) for individuals with SCI has been reported at approximately 22 % [71]. Reports note a higher incidence of gastroesophageal reflux and hiatal hernia in persons with spinal cord injury greater than 5 years duration [72].

Esophageal motor dysfunction carries tremendous clinical implications regarding the risk of aspiration, inflammation, and ulceration that accompanies deglutition or esophagogastric reflux, yet there are relatively few reports addressing esophageal function following SCI [68, 69]. Based upon the neurophysiology of the esophagus, it is imperative to note that GERD in the able-bodied is emerging as a complex interaction of altered esophageal sensory and motor neurocircuitry [73]. This is likely to be exacerbated following damage above the levels of the spinal cord receiving dorsal root ganglion projections from the esophagus.

16.3.1.5 Clinical Presentation

Unlike the able-bodied population, the perceived visceral sensations that accompany GERD (e.g., heartburn, chest spasm and regurgitation) are largely underappreciated and, therefore, infrequently reported to health-care providers [69, 71, 72]. The prevalence of a supine or reclined posture in higher-level paraplegia or tetraplegia may increase the incidence of GERD however quantitative evidence for such a predisposition is lacking. Subsequently, histological and endoscopic evidence of GERD is frequently necessary for a conclusive diagnosis [70].

16.3.1.6 Clinical Evaluation and Treatment

A patient's taken history alone can be diagnostic for GERD. Testing may include empiric therapy with acid suppression and follow-up for evaluation of resolution of symptoms. If the diagnosis of GERD is unclear or empiric therapy with proton pump inhibitors fails, PH monitoring and evaluation of obstruction, anatomic deformity causing disruption of the gastroesophageal tract, and evaluation for a hiatal hernia may be considered [67–76]. Upper gastrointestinal endoscopy may be ordered for concern of dysphagia, a high risk for developing histopathology including esophageal adenocarcinoma (e.g., Barrett's esophagus), or failed acid-suppression therapy [74]. Manometric studies may be done for evaluation of esophageal dysmotility (see [66, 75]).

16.3.1.7 Preclinical Evidence

The motor programs for esophageal reflexes involve integrative circuits incorporating the trigeminal nerve (CN V; muscles of mastication), facial nerve (CN Vll; facial muscles, salivary glands, and mucous membranes of soft and hard palate), glossopharyngeal nerve (CN lX; parotid salivary gland and pharynx), vagus nerve (CN X; the tongue, soft palate, pharynx, larynx, and esophagus), and hypoglossal nerve (CN Xll; extrinsic musculature of the tongue) that reside within the brainstem. Each of

these circuits remains anatomically intact following SCI. Exception to this would be in the scenario of traumatic or nontraumatic facial and head nerve injuries such as in polytrauma, radiation treatment, or postsurgical interventions. Thus, the prevalence and potential mechanism of esophageal dysfunction after human SCI remain largely unresolved, and no studies modeling the presentation of esophageal dysfunction following experimental SCI have yet emerged.

16.3.2 Gastrointestinal Bleed

Gastrointestinal bleed following SCI is most often associated with gastroduodenal ulceration [76]. Peptic ulceration has been frequently reported following traumatic injuries requiring intensive care [77, 78]. Gastrointestinal bleeding is more prevalent in patients with cervical or high thoracic lesions and has increased frequency in complete injuries [76, 79, 80]. Rates can be as high as 5.5 % in this population [81]. Though variable in studies, the rates of gastrointestinal hemorrhage are similar in traumatic (2.5 %) versus nontraumatic etiologies (2.6 %; [82]).

16.3.2.1 Clinical Presentation

Presentation is often insidious when chronic or abrupt because of the lack of early symptoms. Hemodynamic instability and cardiopulmonary decline are common presenting signs. Upper gastrointestinal bleed (UGIB) classically presents with hematochezia and black tarry stools but, if massive, can also present with bright red blood per rectum. Lower gastrointestinal bleed (LGIB) classically presents with maroon stools (right side of the colon), bright red blood per rectum (left side of the colon), and melanic (rectocecal). Gastrointestinal hemorrhage as a result of perforation may initially go unnoticed until there is clear hemodynamic instability [83]. Localization must be done clinically initially, which can be difficult without patient symptoms for guidance.

Provocating factors are multifactorial and likely include plasma stress hormone-mediated ulceration, diminished supraspinal controls leading to unopposed parasympathetic dysfunction, gastric vascular changes, oxidative stress, as well as the controversial use of steroids for treatment of SCI. While there is some evidence against steroids causing gastrointestinal bleed in SCI [79], high-dose steroids are frequently cited to place the stomach at increased risk of ulceration and hemorrhage in human and animal studies [84–86]. In a retrospective case controlled study, the rate of gastrointestinal hemorrhage in SCI was 2.77 % with 33 % mortalities while receiving high-dose steroids, while there were none in the control group [85]. This prevalence is similar to previously reported rates of 1.9–3.5 % depending on low or high doses of dexamethasone [87].

16.3.2.2 Clinical Evaluation and Treatment

Emergent attention to hemodynamic stability and cardiopulmonary monitoring are required. Identification of the location of the hemorrhage can be categorized as upper and lower gastrointestinal source. When upper gastrointestinal bleed (UGIB)

is suspected, upper gastrointestinal endoscopy is the test of choice [88]. When lower gastrointestinal bleed (LGIB) is suspected, fiber-optic flexible colonoscopy is the initial diagnostic tool of choice. Further evaluation would depend on the outcome of initial testing and suspected source [89].

Treatment follows current standard practice for the anatomic location and underlying etiology of the GIB [88, 89]. Stress ulcer prevention with appropriate prophylaxis can reduce the rates of gastritis leading to hemorrhage. The prophylactic administration of proton pump inhibitors or histamine-2 receptor antagonists is widely employed in the intensive care unit and may minimize this particular comorbidity, though whether such practices are justified remains controversial [90, 91]. There is also evidence suggesting that utilizing early nutrition with oral or total parental nutrition to meet the patient's total energy requirements will reduce the ulceration rate [92, 93].

16.3.2.3 Preclinical Evidence

Studies of gastrointestinal bleed following experimental SCI are limited. Animal models have employed low cervical spinal cord transection to provoke ulcerogenesis rapidly within 6 h post-injury [94–97], though a systematic investigation of the mechanisms provoking ulcerogenesis in experimental contusion models of SCI have not been performed.

16.3.3 Gastrointestinal Dysmotility

16.3.3.1 Neurophysiology

The principal functions of the stomach involve (1) a reservoir component for ingested solids and liquids. (2) reduction of the size of food particles through both digestive secretions and the mechanical milling evoked by gastric contraction and relaxation, and (3) the feedback-mediated propulsion of ingesta into the duodenum. The gastric compartment can be subdivided into the fundus, which serves as reservoir and regulates intragastric pressure, and the more muscular corpus where food is milled until reduced in size in order for contraction of the antrum to facilitate passage through the pylorus leading to the duodenum. The principal functions of the proximal duodenum include (1) neutralization of acid in the chyme delivered from the stomach, (2) enzymatic reduction of particles to simple molecules, (3) passive or active absorption of nutrients across the gastrointestinal wall, and (4) peristaltic movement of intestinal contents.

Unlike the organized patterns of digestion produced within the small and large intestines, the enteric nervous system innervating the stomach lacks the capacity to independently control the moment-to-moment changes necessary for appropriate receptive relaxation reflexes, associated with swallowing, as well as gastric milling and/or emptying reflexes. Considerable evidence has accumulated demonstrating that the proximal portion of the gastrointestinal tract is under direct modulation by extrinsic neural circuits. This parasympathetic neural input is in the form of vago-vagal reflex circuits that dominate gastric function, while sympathetic inputs to these target organs are largely confined to regulation of vascular beds and smooth muscle sphincters by indirect modulation through the enteric nervous system. Considerable

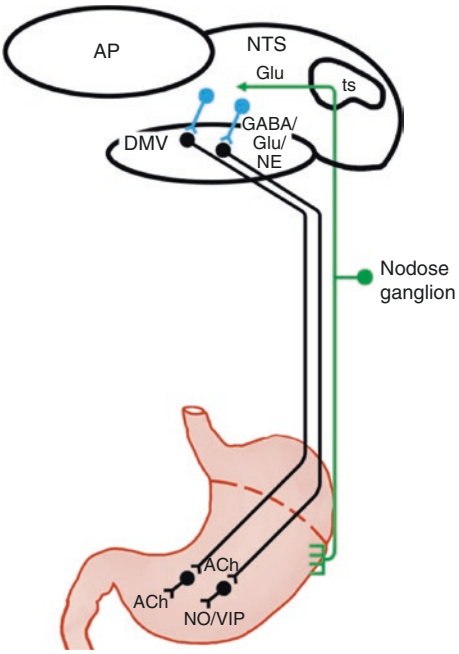

Fig. 16.4 Schematic representation of the gastrointestinal sensory signals that are transmitted to the brainstem by vagal afferent fibers distributed throughout the proximal GI tract. Cell bodies for these vagal afferents reside within the nodose ganglion. Vagal afferents enter the brainstem by way of the tractus solitarius (*ts*) and terminate onto second-order neurons within the nucleus tractus solitarius (*NTS*) principally as a glutamatergic (*Glu*) synapse. At the level of the NTS, converging projections from higher CNS centers (not pictured) are integrated and relayed by NTS neurons to regions which include the parasympathetic preganglionic neurons of the dorsal motor nucleus of the vagus (*DMV*). The neurochemical phenotypes of these NTS projections are predominantly GABA, glutamate, or norepinephrine (*NE*). Together with the area postrema (*AP*), the NTS and DMV form the region of the dorsal vagal complex. Preganglionic DMV motor neurons innervate gastric enteric neurons through two competing pathways. Activation of one pathway initiates a cholinergic (*ACh*)-mediated excitation of gastric smooth muscle which is necessary for gastric tone and motility. Alternatively, activation of a non-adrenergic, non-cholinergic (*NANC*) pathway exerts a profound gastric relaxation through the release of nitric oxide (*NO*) or vasoactive intestinal polypeptide (*VIP*). Reduction in gastric tone and motility, therefore, can be produced by either the withdrawal of excitatory cholinergic drive or the activation of NANC-mediated inhibition. The dashed line on the stomach arbitrarily indicates the transition between the fundus (orally) and the corpus (caudally)

feedback mechanisms exist between the antrum, pylorus, and duodenum for the delivery of chyme in a manner that does not exceed the digestive capacity of the small intestine [98, 99]. These mechanisms are certainly affected by diminished gastric emptying and dysregulation of antroduodenal coordination [100]. As described above, following normal exposure to both the appropriate composition of reduced food particles and the rate of transpyloric delivery of chyme, the duodenum releases gastrointestinal peptides and hormones that are integral to these feedback mechanisms [101–103]. Specifically, gastric reflex function is integrated by circuits within the brainstem dorsal vagal complex (Fig. 16.4), which comprises the area postrema, the nucleus tractus solitarius, and the dorsal motor nucleus of the vagus [104].

The dorsal vagal complex contains the vagal gastric neurocircuitry that serves as an integrative hub for activity that is the result of inputs originating from higher central nervous system areas [105–107], from spinosolitary inputs [108–110], as well as from neurohormonal signals from the periphery. Neurohormonal signaling occurs as a result of the fenestrated capillaries within the dorsal vagal complex that permit diffusion of circulating neuromodulators across a "leaky" blood-brain barrier [111]. All of the signals integrated within the dorsal motor nucleus of the vagus finely tune the coordinated emptying of nutrients from the stomach by way of an interaction between two separate postganglionic circuits under the influence of the dorsal motor nucleus. The parasympathetic preganglionic vagal motoneurons comprising the efferent limb of the vago-vagal reflex are cholinergic and activate postganglionic neurons via actions at a nicotinic receptor. Gastric projecting neurons within the dorsal motor nucleus of the vagus exhibit a basal rate of spontaneous firing [112–114], and it is this low frequency firing which regulates an excitatory (cholinergic) circuit that ultimately promotes the antral milling of ingested solids and the delivery of reduced particles to the duodenum [115].

Gastric relaxation can occur as a consequence of inhibiting this tonically active excitatory pathway [39, 116–119]. Conversely, activation of a non-adrenergic non-cholinergic (NANC) inhibitory vagal projection to the stomach elicits a direct inhibition of gastric motor functions. While this inhibition is often attributed to the release of nitric oxide [39–42, 120–122], purinergic and vasoactive intestinal polypeptide mechanisms have also been identified [31, 41, 123].

16.3.3.2 Clinical Presentation

The majority of reports in the clinical literature describe derangements in upper gastrointestinal reflex emptying and motility, especially after spinal cord injuries occurring above the mid-thoracic spinal segments [70, 100, 124–130]. In extreme cases, the high degree of gastric feeding intolerance demonstrated by these patients necessitates aggressive nutrient supplementation through enteral, parenteral, or invasive surgical interventions in order to maintain positive energy and nitrogen balance [12, 13, 131, 132]. Despite these clear alterations, the mechanisms for gastric reflex dysfunction remain poorly characterized and inconsistently managed in the clinic.

16.3.3.3 Clinical Evaluation and Treatment

Recent technologies permit noninvasive assessment of gastrointestinal dysmotility without radioisotopes [130, 133], though there is no indication that such technologies are routinely employed in clinical settings. Early studies on the effects of SCI on small intestinal function reported orocecal transit times using hydrogen breath testing [128, 134]. While this technique revealed delayed mouth-to-cecum transit times, the technique does not provide clear distinction between reduced gastric emptying and intestinal peristalsis. Determination of specific changes in intestinal motility patterns were not achieved until an orally ingested magnetic tracer was employed [7]. These authors replicated the observed reduction in orocecal transit time, though intestinal contractility was unaffected. This latter observation was

attributed to enteric-mediated smooth muscle activity. A small sample study of SCI subjects revealed a delay in gastric emptying of solids using the noninvasive [^{13}C]-octanoate breath test [135].

The reflex control of the stomach is under considerable modulation by a wide range of gut hormones [136]. Despite long-established evidence regarding the role of gastrointestinal hormones in nutrient ingestion and passage throughout the gut, the evaluation of this important regulatory system in the spinal cord-injured population is scarce. Motilin, a 22-amino-acid peptide released from the upper intestine, stimulates gastric and intestinal myoelectric activity during phase III contractions of the migrating myoelectric complex of the interdigestive phase. Comparisons of serum motilin levels in a limited sample of uninjured, paraplegic, and tetraplegic subjects revealed that motilin levels were largely similar across all three groups, though there was a trend toward elevated motilin levels in the paraplegic group [137]. Peptide YY is a 36-amino-acid peptide hormone that is similar to gastrointestinal peptides pancreatic polypeptide and neuropeptide Y that is released from epithelial cells within the ileum and colon. However, the actions of circulating peptide YY target the upper GI as an "ileal brake" whereby peptide YY potently diminishes gastric acid secretion, gastric emptying, intestinal propulsion, and pancreatic exocrine secretion [102]. In this same study described above, levels of peptide YY in chronic SCI individuals were similar in the fasted state but were significantly elevated in the early postprandial state of tetraplegic subjects [137]. The limited sample size and the absence of essential physiological parameters, such as gastric emptying rates during the postprandial serum measurements, limit the interpretation of these findings and merit reevaluation in a larger sample from the SCI population. Finally, the neurohormone ghrelin, previously described as being secreted from oxyntic cells within the gastric mucosa [138, 139], is upregulated during periods of negative energy balance, such as before meals, and is downregulated after feeding [140]. Furthermore, there are structural and genetic similarities between ghrelin and motilin receptors [141], though there is no cross talk between the respective ligands [142, 143]. The clinical utility of ghrelin and ghrelin mimetics as an endogenous therapeutic target has garnered widespread attention for the treatment of gastrointestinal motility disorders [144]. A study of uninjured, paraplegic, and tetraplegic individuals reported no differences in levels of serum ghrelin across all groups following an overnight fast [145]. Unfortunately, with the exception of a study on eating attitudes [146], clinical evidence regarding the dietary behaviors of the spinal cord-injured population is lacking. In contrast to the spinally intact clinical population, studies regarding the orexigenic and promotility responses to exogenous ghrelin following SCI are nonexistent.

16.3.3.4 Preclinical Evidence

Animal models of spinal transection or studies employing an established model of contusion SCI [147] are beginning to reveal similarities in gastric dysmotility between rodent models and that reported for humans. Expanding upon the initial reports that high thoracic spinal transection delayed the emptying of a liquid test

meal [148, 149], diminished food intake has been reported in chronic T3-SCI rats [150]. Further physiological studies have recorded circular smooth muscle contractions [151] at rest, in response to pharmacological challenge, and following elicitation of the esophagogastric reflex [152]. Using techniques to elicit this reflex following T3-SCI, physiological distension of the esophagus failed to elicit a reflex relaxation of the stomach [153]. This impaired accommodation reflex may contribute to dysphagia and reflux of ingested matter and early postprandial fullness. Furthermore, this reduction in gastric reflex activity was not altered by sympathectomy [153]. These results were in agreement with earlier conclusions that post-SCI dysmotility was mediated through possible alterations in the anatomically intact vagal neurocircuitry [149].

Studies using [^{13}C]-octanoate-tagged solid meals in order to indirectly measure gastric emptying in awake animals confirmed that gastric dysmotility is accompanied by a delay in gastric emptying and that both diminished gastric emptying and dysmotility persist up to 6 weeks after T3-SCI [154]. These persistent deficits suggest that delayed gastric emptying is unlikely to be due to "spinal shock" as gastric dysmotility persists long after experimental spinal cord injury animals are generally considered to have stabilized (ca. 3–6 weeks post-injury).

Circulating cholecystokinin has been implicated in stimulation of the gall bladder, pancreas, and gastrointestinal motility (reviewed in [136]). It is also produced by a number of neurons within the central nervous system and is implicated in feeding behavior and nociception. No evidence is available in the clinical literature regarding cholecystokinin function following spinal cord injury; however, experimental studies have tested the sensitivity of vagally mediated gastric reflexes in T3-SCI rats [155]. In regard to gastrointestinal actions, it is well accepted that peripheral cholecystokinin activates C-type vagal afferent fibers that project to nucleus tractus solitarius cells [156–158]. Study of experimental SCI was particularly revealing in that peripheral administration of the sulfated cholecystokinin octapeptide (CCK-8 s) 3 days after injury induced significantly less activation in the nucleus tractus solitarius than in uninjured control rats [155]. In the same experimental animals, *c-Fos* expression within the adjacent area postrema was similar in both groups, suggesting that gastric neurocircuitry involving the nucleus tractus solitarius was selectively impaired. Previous experimental studies suggest that in addition to peripheral effects upon vagal afferents within the gastrointestinal tract, cholecystokinin acts directly upon brainstem vagal circuits [159–166]. However, T3-SCI rats did not demonstrate a gastric efferent vagal response to central microinjection of CCK-8s into the DVC, and the reduced sensitivity to centrally administered CCK-8s in the DVC persisted at 3 weeks after injury [155]. These data also support the hypothesis that post-injury dysmotility is mediated through alterations in gastric vagal neurocircuits.

In experimental studies, ghrelin is known to exert stimulatory effects upon gastric motility and acid secretion as well as food intake and energy metabolism [167–171]. This stimulatory effect occurs in both fed and fasted states [172, 173]. A central inhibitory effect of ghrelin has been reported for fundic tone of fed animals [171], whereas an excitatory effect has been demonstrated *in vitro* within

brainstem vagal neurocircuits and *in vivo* with gastric corpus contractions in fasted animals [174]. Similar to the observations for cholecystokinin following experimental SCI, emerging studies with peripheral and central administration of ghrelin also reveal a reduced sensitivity within the nucleus tractus solitarius of T3-SCI rats [175, 176].

The common feature of these aforementioned animal studies is the diminished sensitivity of gastric projecting vago-vagal reflex circuits to important gastrointestinal peptides. As described above, and for any neural reflex circuit, vago-vagal control of gastric motility is regulated by afferent and efferent limbs, and dysfunction in either of these limbs will impair proper gastric function. Recent data has provided convergent anatomical, neurophysiological, and functional evidence for the integrity of gastric-projecting dorsal motor nucleus of the vagus neurons in acute T3-SCI rats [177].

In summary, the apparent reduction in gastric vagal afferent responsiveness to mechanical and chemical stimuli suggests a generalized hyposensitivity of vagal afferent neurotransmission to the brainstem following SCI. Evidence of vagal afferent hyposensitivity has been identified in other GI pathophysiological states [178, 179]. In particular, Xue and colleagues suggest that part of the diminished visceral afferent sensitivity in an inflammation-induced model of functional dysmotility is mediated through an inducible nitric oxide synthase (iNOS) mechanism [179]. While this observation was limited only to afferents within the mesenteric arcade and did not include the vagus, emerging evidence supports specific vagal hyposensitivity following experimental SCI [180].

16.3.4 Gastroenteritis

One implication of delayed orocecal transit in the spinally injured individual is the possibility of small intestinal bacterial overgrowth. The association between bacterial overgrowth and functional gastrointestinal disorders, specifically those that are not linked to neurotrauma, remains controversial [181]. However, the role of the gastrointestinal microbiome in health and disease states is rapidly advancing, and the interactions between nutrient composition, gastrointestinal transit, and the microbiome have only recently started to be explored [182]. Gastroenteritis in SCI patients can be viral or bacterial in nature. While no incidence of either cause has been elucidated, it was determined in one small cross-sectional cohort that 50 % of patients were carriers for *Clostridium difficile* and 55 % for vancomycin-resistant *Enterococcus* (VRE).

16.3.4.1 Clinical Presentation

The traditional response of infection on the gastrointestinal system can be blunted or exaggerated and often masked by lack of sensation [183]. The impact of gastroenteritis is measured in the clinical treatment and the persistence of bowel incontinence. In one epidemiologic study, 62 % of SCI patients as compared to 8 % of normal subjects reported a decrease in quality of life due to fecal incontinence [184].

Symptoms may include devastating results to continence in the form of total fecal incontinence or changes in stool patterns. Clinical signs may or may not be associated with fevers and chills. Autonomic dysreflexia could easily be the presenting symptom for gastroenteritis. Pain will be variable depending on the level and degree of impairment of sensation. It may include referred pain from the abdomen such as shoulder pain or may present as bloating pain in the abdomen. The physical exam may indicate a spastic abdomen with hyperactive bowel sounds. Conversely, there can also be distention of the abdomen with decreased bowel sounds, which in one case report was associated with *Clostridium difficile* colitis [185].

16.3.4.2 Clinical Evaluation and Treatment

Gastroenteritis management and treatment should typically follow current institutional standard practice for the underlying etiology (cf., [186]). Treatment must involve adequate hydration as many chronic SCI patients fluid-regulate to control catheterization volumes, which can put them at risk for dehydration if output is pathologically increased. Additionally, cessation of laxatives in a non-constipated patient is advisable. If bacterial, treatment should be focused on appropriate treatment of *C. difficile* with metronidazole or oral vancomycin or of VRE with linezolid. If the stool is profuse, a fecal collection system can be employed, and in rare cases, a rectal plug is considered. Surgery is only considered in severe cases of colitis.

If the patient received antibiotics recently, a high suspicion for *C. difficile* remains, and stool analysis should be performed. An abdominal plain radiograph can be used to evaluate the stool burden in chronic constipation and air-fluid levels in small bowel obstruction. Infection by *C. difficile* and pseudomembranous colitis may occur more often in SCI patients treated with trimethoprim-sulfamethoxazole. Contact precautions are necessary for prevention of spread of infection to other populations when the patient is hospitalized. Precautions for *C. difficile* include handwashing because of the decreased ability of alcohol sanitizers to adequately kill the spores.

16.3.5 Neurogenic Bowel (Upper Motor Neuron)

16.3.5.1 Neurophysiology

The colon, rectum, and the internal anal sphincter form an integrated unit for the final digestive processing, storage, transport, and elimination of gastrointestinal contents (reviewed in [187, 188]). As with the upper gastrointestinal tract, smooth circular and longitudinal muscle layers serve either to mix or to propel luminal contents toward the distal-most rectum. Continence is primarily maintained by the resting tone of the smooth muscle of the internal anal sphincter (IAS) and is augmented by contractions of the striated external anal sphincter muscle. The contribution of distal GI tract anatomy and associated pelvic floor musculature that is particular to a given species (especially humans) serves to further augment continence

mechanisms by the mechanical alteration of the rectum. In the laboratory rat, pelvic floor muscles such as the levator ani are not involved in defecation reflexes [189], whereas a role for the iliocaudalis and pubocaudalis, beyond a hypothesized model for pelvic organ prolapse [190], remains to be determined.

Although the reflexes involved in defecation control appear to be mediated by sacral segmental circuits, their form, magnitude, and coordination appear highly dependent on descending input from rostral CNS structures. Anal sphincter reflexes are compromised in patients with spinal cord dysfunction, suggesting an important descending or spino-bulbo-spinal component [191]. These patients also exhibit chronic constipation and impaction, which has been attributed, in part, to excessive contractions of the external anal sphincter and dyssynergia with actions of the internal anal sphincter [192]. Similar difficulties with micturition and urethral sphincter musculature are well documented [193]. Clinical evidence suggests that caudal brainstem structures may mediate rectoanal inhibition in that colonic inertia and a loss of rectoanal inhibitory reflexes occur in patients with posterior brainstem lesions [194].

Enteric innervation of the IAS is through a continuation of rectal wall ganglion cells rather than local ganglion cells ([195] cited in Krier [196]). As such, the major innervation of the IAS is through both sympathetic and parasympathetic control. Anorectal sympathetic innervation originates in the autonomic nucleus of the lumbar spinal cord (refer to Fig. 16.2). Numerous preganglionic sympathetic fibers terminate in the inferior mesenteric ganglia and the pelvic plexus, the latter receiving sympathetic input by way of the hypogastric nerve originating in the inferior mesenteric ganglion [196]. Hypogastric nerve stimulation results in an increase in IAS pressure [197]; however, hypogastric-mediated sympathoexcitation of the IAS has been reported to occur only in response to supramaximal levels of the rectal stimuli necessary to evoke the rectoanal inhibitory reflex [198]. The preganglionic parasympathetic innervation of the IAS is through the pelvic nerves [196, 199]. The pelvic nerves modulate both cholinergic and non-cholinergic excitatory as well as non-adrenergic and non-cholinergic inhibitory postganglionic fibers to the rectum and IAS.

16.3.5.2 Clinical Presentation

Neurogenic bowel refers in particular to colonic dysfunction that presents as reduced colonic transit, constipation, disordered evacuation reflexes, and potential incontinence. By virtue of the parasympathetic and somatic neural circuitry located within the sacral spinal cord, neurogenic bowel is a common gastrointestinal disorder accompanying traumatic and nontraumatic SCI. Despite widespread recognition of diminished quality of life stemming from constipation and overflow incontinence, previous reviews of the literature reveal that individuals with spinal cord dysfunction are still offered interventions in response to neurogenic bowel rather than substantial evidence-based or preclinical data (see [200]).

In addition to the necessity of tetraplegics to rely upon assistance from caregivers regarding bowel management, the inordinate amount of time spent on bowel care by many SCI individuals is often cited as a primary factor in patient dissatisfaction and diminution of quality of life [201]. Various options are offered to individuals and

range from conservative and noninvasive strategies to surgical treatments [202]. Taken as a whole, these strategies generally offer guidelines for tailoring a bowel management program to meet individual needs.

Recommendations for optimizing diet and fluids provide the most universal management protocol and are applicable in health and disease. Rectal chemical stimulants containing glycerine alone, or in combination with other agents, are commonly used to promote contractile and secretory processes within the colon due to the ease of administration and timing of effect. Oral pharmacological stimulants to promote both peristalsis (e.g., bisacodyl) and/or stool softening may be of limited value due to the rate of onset of effect in a population with diminished or absent rectoanal sensation and ability to maintain voluntary muscle control to aid in continence. Transanal irrigation offers another nonsurgical technique that is reported to be well tolerated [203]. If the individual retains reflexive anorectal-colonic function, digital rectal stimulation may be employed to promote reflex peristalsis and achieve evacuation. In more extreme instances, digital rectal evacuation may be necessary in order to actively remove impacted feces.

Numerous surgical interventions have been identified for more refractory bowel dysfunction. Antegrade continence enemas require a necessary surgical procedure as described by Malone and colleagues [204]. The long-term efficacy and stability of this technique remains poorly explored for the spinally injured population. While the precise mechanism and degree of efficacy for sacral stimulation on neurogenic bowel remains unclear [205], some degree of patient satisfaction has been reported [206, 207]. Colostomy or ileostomy offers greater ease of management and a high degree of satisfaction [208], and recent reports indicate that postsurgical complications and morbidity do not differ from able-bodied patients [209].

For most, if not all, of the procedures listed above, caution must always be exercised in individuals with injuries above T6 regarding triggering of autonomic dysreflexia in both poorly managed and aggressively managed neurogenic bowel [210].

16.3.5.3 Preclinical Evidence

As described previously, the enteric nervous system is capable of independently regulating gastrointestinal contractility and secretion through intrinsic neural circuits that process sensory information, relay that information through interneuronal pools, and ultimately effect activation of motor efferents [196, 211]. When separated from extrinsic input, these intrinsic reflexes are sufficient to set a basic pattern of contractility within the rectum and internal anal sphincter [212]. *In vitro* and *in vivo* recordings of IAS muscle reveal an increasing frequency gradient along the oral-aboral extent of the IAS that is substantially higher than that recorded within the rectum [213, 214]. The magnitude of intrinsic nervous system reflexes appears to be complemented by an extrinsic parasympathetic reflex [215], though the relative importance of either intrinsic or extrinsic rectoanal reflexes during defecation remains to be determined.

Studies in rodents have revealed the existence of descending inputs to the spinal neurocircuitry responsible for defecation reflexes [216, 217]. This pudendal circuitry principally consists of the somatic motoneurons innervating the external anal

sphincter located dorsomedially in the lumbosacral ventral horn and preganglionic neurons in the sacral parasympathetic nucleus located laterally in the intermediate gray matter [217–220]. Studies that employed retrograde tracers unilaterally injected into the lumbosacral ventral horn region of the spinal cord identified projections from the nucleus raphe obscurus, raphe magnus, raphe pallidus, and lateral nucleus paragigantocellularis [221]. Utilizing this data, anterograde tracer injections were made into the nucleus raphe obscurus [218] or lateral nucleus paragigantocellularis [219] in animals that also received retrograde tracer injections into the external anal sphincter. These studies demonstrated nucleus raphe obscurus and lateral nucleus paragigantocellularis terminal appositions on external anal sphincter motoneurons, which are the only descending projections to the external anal sphincter that have been identified to date.

Physiological experiments have demonstrated that brainstem stimulation reduces anal sphincter reflexes [222] and that after complete spinal cord transection, a persistent hyperreflexia develops that may parallel human SCI [223]. After partial spinal cord contusion lesions, rats recover bowel reflexes over a period of several weeks, depending upon the severity of the lesion [224, 225]. Further research has revealed that the recovery curves for these reflexes (when observed at 3 days, 1, 3, and 6 weeks after surgery) correlate with the optical density of immunofluorescent-labeled serotonergic fibers [225]. These lesions spare some immunolabeled serotonergic axons traversing past the lesion center and are hypothesized to provide the substrate by which serotonergic sprouting may occur in the lumbosacral spinal cord. The most likely candidates for these fibers are the previously identified projections from the nucleus raphe obscurus and the rostral gigantocellular reticular nuclei complex [218, 219]. Functionally, both brainstem nuclei seem to inhibit some pudendal reflexes in that the rostral gigantocellular reticular nuclei complex may have a greater effect upon the bulbospongiosus motoneurons involved in sexual reflexes [226–230] and the nucleus raphe obscurus may have a greater effect upon external anal sphincter control since lesions of this nucleus produce a transient ano-anal reflex increase [231].

16.3.6 Neurogenic Bowel (Lower Motor Neuron)

As previously described above, the reflex control of defecation is mediated by sacral segmental circuits. Therefore, lesions of the conus medullaris or sacral roots provoke a lower motoneuron sign with diminished parasympathetic and somatic tone to the internal and external anal sphincters, respectively. Furthermore, smooth muscle tone of the descending colon and rectosigmoid apparatus is also diminished such that extrinsic reflex peristalsis and propulsion of feces is absent. The sensory limb of the pelvic floor reflex arc is also anatomically compromised, leaving only enteric-mediated reflexes. Therefore, unlike upper motor neuron dysreflexia that may result in overflow incontinence, flaccid paralysis accompanying lower motor neuron damage results in passive incontinence and leakage [232]. Regardless of the mechanism, the potential for incontinence in social settings provokes tremendous anxiety in injured individuals and may lead to social isolation.

16.4 Additional Digestive System Comorbidities for Clinical Consideration

16.4.1 Pelvic Pain

16.4.1.1 Neurophysiology

The innervation of the viscera, in contrast to innervation of cutaneous and joint origin, is diffuse. Though visceral afferents reach the spinal cord through sympathetic and parasympathetic nerves, these fibers have their cell bodies within the dorsal root ganglia and are not components of the autonomic nervous system. In addition, visceral sensory fibers terminate bilaterally over multiple spinal segments [233] and, when coupled with the convergence of spinal inputs of visceral and cutaneous origin onto dorsal horn nociceptive circuits, lead to the phenomenon of referred pain (as in thoracolumbar referral to pelvic and abdominal referral to pelvic) and can lead to complex evaluations (Table 16.2).

In a chronic pain study, a 5-year follow-up of post-traumatic SCI reported visceral pain (that which was localized or appeared related to the abdominal pathology) that had the longest time of onset, estimated slightly greater than 4 years in comparison to musculoskeletal or neuropathic pain [234]. In a study of adults with chronic pain following traumatic spinal cord injury, 37.6 % reported pain located in the pelvic girdle (visceral or musculoskeletal pain) with no sex-based differences. When compared to other types of chronic pain (upper and lower limbs), pelvic girdle pain was rated as the most severe. Pelvic girdle pain was noted to occur with cervical, thoracic, and lumbosacral levels of injury with the highest reported among persons with lumbosacral levels of injury [235].

16.4.1.2 Clinical Presentation

Systematic evaluation of the cause of pelvic pain is warranted, but the challenge is in identifying the source in the setting of incomplete or complete nerve injuries. Pelvic pain could be categorized by where the anatomic source the pain is arising from: gynecological, urological, gastrointestinal, musculoskeletal, or referred sources of pain (Table 16.3). This section will focus on gastrointestinal sources of pain. Gastrointestinal sources of pelvic pain may include bowel distension, bowel impaction, visceral ischemia or perforation, irritable bowel syndrome, inflammatory bowel disease, GI instrumentation, trauma, intra-abdominal cavity tumors, endometriosis, adhesions, bleeding, and infection. On occasion, pelvic with concurrent abdominal pain may originate from neither viscera nor cavity but rather from neural dysfunction within the thoracolumbar spinal cord causing a “band-like” neuropathic pattern of superficial pain [236].

16.4.1.3 Clinical Evaluation and Treatment

Physical exam may reveal abnormal vital signs, cachexia, non-localizing pain on abdominal or pelvic region palpation, and reduced urine output. In addition to a gastrointestinal exam, gynecologic, genitourinary, and musculoskeletal exam of the back and pelvic girdle and skin exams are done to complete the evaluation

Table 16.2 Differential diagnoses for referred visceral pain

Evaluation of	Differential diagnoses
Vague abdominal discomfort with nausea	Myocardial Infarction Ulcer Cholelithiasis Constipation Obstipation Lactose intolerance Gastroenteritis Ileus Colitis GI hemorrhage Post-abdominal procedural complications Superior mesenteric artery syndrome Renal or bladder stones
Postprandial discomfort	GERD GI ulcers Acute and chronic cholecystitis Cholelithiasis Acute and chronic pancreatitis Lactose intolerance Gastroenteritis Ileus Colitis Irritable bowel syndrome Mesenteric ischemia or infarction Bowel obstruction Benign and malignant masses Post-abdominal procedural complications Superior mesenteric artery syndrome

(Table 16.2). When gastrointestinal sources of pelvic pain are suspected, initial evaluation may include plain abdominal and pelvic radiographs and serologies.

In acute pain, medical and surgical treatment depends on the underlying organic condition such as bowel distension, bowel impaction, visceral ischemia or perforation, GI instrumentation, trauma, intra-abdominal cavity tumors, bleeding, and infection. If the patient is in autonomic dysreflexia (AD) during the evaluation, procedures for the treatment of AD are concurrently followed (e.g., [237]; Table 16.3).

In chronic pain, determining the effective treatment may become challenging and require multimodal regimens and multidisciplinary and interdisciplinary approaches. The rehabilitation team may include multiple medical-surgical clinicians, physical and occupational therapists, neuropsychologists, nutritionists, and care coordinators in collaboration with the patient and caregivers. For gastrointestinal sources in chronic pelvic pain, treatment is focused on the underlying condition which may be irritable bowel syndrome, inflammatory bowel disease, endometriosis, adhesions, post-trauma, and post-GI instrumentation. If analgesics are considered in the treatment regimen, target is toward the clinical features such as pain

Table 16.3 GI causes of pelvic pain

Bowel distension
Bowel impaction
Visceral ischemia or perforation
Irritable bowel syndrome
Inflammatory bowel disease
Intra-abdominal cavity tumors
Endometriosis
Adhesions
Hemorrhage
Infection (GI or spread from pelvis)
GI interventional procedures
Trauma
Neuropathic pain pattern originating from the thoracolumbar spinal cord

chronicity and concomitant acute component, persistent or stimulus provoked hyperalgia, musculoskeletal and neuropathic pain, and history of responses to prior and current medications. Sacral nerve modulation through sacral nerve stimulation (SNS) trials and spinal cord stimulators has been reported to reduce pain. SNS also can be part of the treatment regimen in urinary or bowel incontinence, if present [238–240]. SNS trials have been reported effective in reducing pain when sacral nerves are intact or have had incomplete injury and not effective in complete sacral injuries. Intractable pelvic pain has been reported with patients following cauda equina syndrome, and pain reduction was reported with SNS [241].

To reduce complications, medical-surgical evaluation of gastrointestinal sources for pelvic pain is warranted given the difficulty of identifying the source of the non-localizing pain in the setting of sensory complete or incomplete injuries of the spinal cord. In patients with injury above or at the sixth thoracic level, disruption and distension of the pelvic and abdominal viscera can trigger spinal viscera-sympathetic reflex pathway of the sympathetic preganglionic neurons causing AD. This complication is a medical emergency and symptoms include uncontrolled hypertension, pounding headaches, flushing of the skin above the spinal cord injury, nasal congestion, bradycardia, profuse sweating, and nausea. Procedures for the treatment of AD are concurrently followed to the evaluation of pelvic pain (cf., [242]).

16.4.2 Postprandial Abdominal Discomfort

16.4.2.1 Clinical Presentation

Postprandial discomfort with GI sources can occur in persons with spinal cord dysfunction and is defined as discomfort after consuming a meal that is separate from discomfort occurring during eating (such as during swallowing, discussed above) or not related to the timing of consuming a meal [243, 244]. The presence of

abdominal discomfort was not associated with the neurological level of the spinal cord injury. Intensity of abdominal pain was not associated with gastrointestinal transit time [245].

Differential diagnoses include the following sources: gastric (ulcers, benign and malignant masses, and gastroesophageal reflux), biliary (acute and chronic cholecystitis, cholethiasis, and benign and malignant masses), pancreas (acute and chronic pancreatitis), and bowel (gastroenteritis, lactose intolerance, ileus, colitis, irritable bowel syndrome, mesenteric ischemia or infarction, and obstruction). Intestinal obstruction could be caused by severe constipation, obstipation, strictures, abdominal compartment syndrome, superior mesenteric artery syndrome, adhesions, post-procedural complications, or benign and malignant masses. Note that colitis and masses typically would be listed as a source of persistent discomfort although they can also present as postprandial discomfort especially if they cause obstruction of food and liquids.

16.4.2.2 Clinical Evaluation and Treatment

Localizing the source of the abdominal discomfort is a challenge due to disrupted ascending sensory tracts, the diffuse distribution of gastrointestinal afferents within the autonomic nerves to the spinal cord (refer to Fig. 16.2), pathophysiological sprouting of sensory projections (described in a previous chapter in this volume), and the multisegmental distribution of afferent terminals. As a consequence, clinicians are not able to rely on standard physical exam characteristics of different pain syndromes. History taking and several key physical exam elements which do not rely on the sensory tracts become even more important [246, 247]. Of note, there are a few abdominal pathologies such as acute cholecystitis, cholethiasis, cancer, and irritable bowel syndrome which do not have history or physical exam findings that exclude them from the abdominal discomfort assessment and, therefore, require further testing [248]. Treatment should follow current standard practice for the underlying etiology (Fig. 16.4)

16.4.3 Superior Mesentery Artery Syndrome

16.4.3.1 Physiology

Superior mesentery artery syndrome is also referred to cast syndrome, arteriomesenteric duodenal compression syndrome, and Wilkie's syndrome. SMA syndrome might co-occur with celiac axis compressions syndrome which is also a rare entity and is due to mesenteric ischemia from celiac axis compression. The pathophysiology of SMA syndrome involves the obstruction of the third portion of the duodenum by the SMA causing proximal duodenal outflow obstruction. The duodenum runs between the SMA and the abdominal aorta. There is a narrow angle of an estimated 45° between these two vessels which has been explained as an anatomic predisposing factor of the compression of the duodenum when precipitating factors arise. Factors that reduce that already narrow angle and compress the duodenum can lead to SMA syndrome. Other reported anatomic predisposing factors include

reduced fat "cushion" between the duodenum and vessels, shorter height, and stiffness of the thoracic curve as seen with bending. There are reports of both congenital and acquired factors. Congenital factors that alter the angular relationship of the duodenum and the vessels predispose the compression. Precipitating acquired factors include BMI ≤ 18, severe rapid loss of mesenteric fat (such as in high catabolic conditions in eating disorders, malabsorption, burns, and cancer), abdominal wall weakness, prolonged colon transit time which can lead to constipation, and postsurgical complications following abdominal or spinal surgery where anatomical alterations could lead to the SMA compression of the duodenum.

16.4.3.2 Clinical Presentation

This syndrome has been reported among patients with SCI [249]. Presentation of superior mesenteric artery (SMA) syndrome might include general discomfort, no bowel movements for over several days, diffuse abdominal discomfort, autonomic dysreflexia, or unexplained increase in tone or spasms after consuming a meal or binge drinking [250]. History might include postprandial nausea, vomiting, early satiety, and indistinct chest discomfort. Complaints of general fatigue and poor oral intake might be the only early symptoms reported. In severe cases, abnormal vital signs include fever and hemodynamic instability.

16.4.3.3 Clinical Evaluation and Treatment

Physical exam findings might include flushing, sweating, teeth erosion, distended abdomen, and abnormal bowel sounds. Palpation of the abdomen might elicit localizing or diffuse pain or be negative. Neurological exam might reveal increased tone or muscle spasms. Rectal exam might show fecal impaction, lesions, masses, or bleeding.

Basic evaluation includes initial basic studies such as complete blood count, chemistries, and flat and upright abdominal films. The literature suggests that determination for when abdominal radiological exams should be performed be based upon at least 2 of 6 of the following history and physical exam elements including distended abdomen, increased bowel sounds, history of constipation, previous abdominal surgery, age over 50, and vomiting. For persons following SCI, these elements are particularly useful as they don't rely on intact sensory fibers which can be injured in SCI. Further evaluation would depend on clinical findings and the suspected source (cf., [251–253]).

Treatment for the source would follow as with non-SCI patients. Precautions would include at least the attention to the patient's sensory and motor deficits below the level of injury, cardiopulmonary and autonomic stability, and skin integrity. Additional precautions would be tailored to the patient.

Treatment includes medical conservative and surgical management. First-line treatment is medical which includes decompressing the dilated gastric region with nasogastric tube, fluid resuscitation, and bowel rest with nutrition delivered parenterally. Side lying after eating helps widens the aorto-mesenteric angle [254]. Surgical treatment involves investigating and relieving the cause of the compression such as intervention for an abdominal mass, aneurysms, spinal deformities, and

other pathological conditions [255]. Literature suggests that laparoscopic duodenojejunostomy is the surgical procedure of choice. Interventions would need to be individualized for the patient [255].

16.5 Areas for Targeted Preclinical Research

A heightened understanding of the cellular and biochemical cascades which follow SCI has emerged over the past 20 years. In that period of time, the scientific community has gained an appreciation of the multifactorial challenges for successful regeneration of damaged tissue and has expended considerable intellectual capital upon the recovery of stepping and standing after injury. By comparison, post-injury changes to the autonomic reflexes of the gastrointestinal tract remain inadequately explored. There exists considerable opportunity for productive preclinical gastrointestinal research in animal models of SCI and the translation of preclinical research into practical clinical and community applications to improve the health and well-being of individuals living with spinal cord dysfunction.

The gastrointestinal motility dysfunction in a spinal cord-injured individual presents a unique clinical scenario that is not similar to any other gastrointestinal motility disorders in an individual with an intact spinal cord. The complete loss of supraspinal inputs to autonomic neural circuits in the spinal cord presents vascular challenges that can impinge on the metabolic function of all affected organ systems. Indeed, emerging evidence has revealed the development of an injury-induced immune deficiency syndrome [256]. This syndrome has implications for the ongoing neurological recovery as well as the overall level of morbidity and mortality of the individual [256–259]. The interplay of dietary habits and the integrity of the gastrointestinal system over the lifespan of an immunodepressed spinal cord-injured individual cannot be overlooked.

Greater understanding of potential changes to the residual enteric and below-level spinal circuitry on gastrointestinal function remains urgent. Perhaps most important is the growing attention autonomic reflexes have gained as functional outcome measures in preclinical research [260]. Therapeutic interventions which fail to realize significant improvement in locomotor function may have long provided promising, yet unrealized, relief of gastrointestinal dysfunction for the population with the spinal cord dysfunction.

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Neurogenic Respiratory Failure

17

Sven Hirschfeld and Roland Thietje

Abstract

A high spinal cord injury (SCI) above the fifth cervical level usually results in a severe impairment of the respiratory function. Paralysis of the muscles needed for respiration, foremost the diaphragm muscle, leads to a significant loss of vital capacity with the need of partial or complete mechanical ventilation. Nearly ten percent of all SCI patients need temporary ventilation during initial treatment directly after the impairment. Six percent of this group are in need of permanent artificial ventilation due to unsuccessful weaning attempts.

In industrialised countries, the incidence and the age of ventilated patients have increased dramatically over the last decade. Older patients often have multiple comorbidities, which prolong the time of primary rehabilitation. The diagnostic procedures and individual therapy of neurogenic respiratory dysfunctions are complex and can only be handled adequately by a multidisciplinary team. Life-long medical support for inpatient and out-of-hospital treatment, the correct application of non-invasive and invasive ventilation, proper adaptation of the weaning regime and the setup of long-term ventilation including implantation of an electrical diaphragm stimulator represent clinical challenges.

A long-term follow-up of ventilated patients regarding complications, life expectancy, mortality and survival rates is needed to allow for the definition of valid standards of care and to achieve a high degree of quality of life in this growing patient population.

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17.1 Introduction

A prerequisite for sufficient ventilation is a preserved diaphragm function. The diaphragm is innervated by nerve roots originating from the spinal cord segments C3 and C4. Therefore, the group of patients with a neurological level of lesion above C5 may be able to breathe spontaneously or require artificial ventilation depending on the exact level of injury. In German-speaking countries, at least 50 % of this group need temporary artificial ventilation [1]. In former times, treatment of patients with an insufficient respiratory function was only possible on intensive care units, and two-thirds of these patients died within the first year. Medical progress has led to a higher number of patients surviving tetraplegia with artificial ventilation (Fig. 17.1) [1]. As a result of advances in technology and patient care, permanent or temporary ventilation can nowadays be handled in out-of-hospital settings. More than 90 % of these patients require invasive ventilation via tracheotomy [2]. The diagnosis and individualised therapy of respiratory dysfunction are complex and require life-long and specialised treatment for inpatient and out-of-hospital treatment according to guidelines. This does not only relate to the setup of both non-invasive [3] and invasive ventilation but also to weaning regimes and long-term ventilation including the implantation of an electrical diaphragm stimulator.

17.2 Epidemiology of Ventilated Patients

In a registry of all German-speaking countries, data on long-term follow-up concerning complications, life expectancy, mortality and quality of life are available for the last 25 years, which allows provision of valid information about patient characteristics, treatments and trends in the population of ventilated SCI patients [4].

In Germany the incidence and the age of ventilated patients have increased dramatically over the last decade [4] (Fig. 17.1). Over the last 13 years, the number of these patients has quadrupled and nearly ten percent of all SCI patients need temporary or permanent ventilation as part of their initial treatment in the hospital [4].

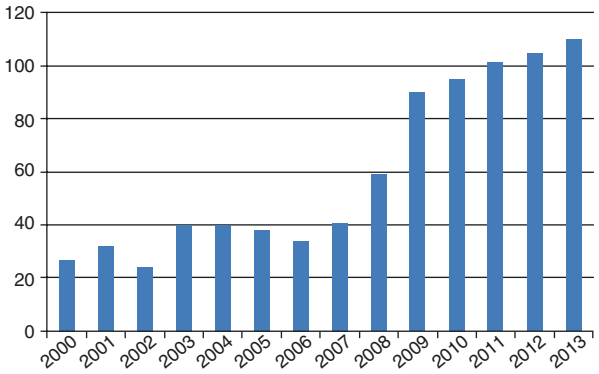

Fig. 17.1 Number of patients in Germany in need of ventilation at the time of hospital discharge

Older patients often have multiple comorbidities, which prolong the time of primary rehabilitation.

In the ventilated patient population, the main causes in case of traumatic SCI are still traffic accidents closely followed by falls. In non-traumatic SCI inflammation, degenerative processes and vessel-related complications are the leading causes (Table 17.1). The most frequent neurological level of lesion is segment C2, while most patients are motor complete (ASIA impairment scale (AIS) A and B in total 87 %) (Tables 17.2 and 17.3). Concerning gender (male = 77.3 %; female = 22.7 %) and mean age at the time of injury (mean age = 43.5 years), the characteristics between non-ventilated and ventilated patients do not differ significantly. Nowadays, patients have a higher age (1997, mean age = 35.4 years; 2014, mean age = 58.2 years) at the time point of injury due to demographic change in industrialised countries.

Table 17.1 Causes of SCI in ventilated patients

Cause of SCI	Percentage (number of cases)
Traumatic:	84.6 % (n = 93)
Traffic	41.8 % (n = 46)
Fall	15.5 % (n = 17)
Work	8.2 % (n = 9)
Diving	5.5 % (n = 6)
Suicide attempt	2.7 % (n = 3)
Leisure/sports	2.7 % (n = 3)
Crime	1.8 % (n = 2)
Other	6.4 % (n = 7)
Non-traumatic	15.4 % (n = 17)
Inflammation	6.4 % (n = 7)
Degenerative	3.6 % (n = 4)
Vessel related	2.7 % (n = 3)
Tumour	1.8 % (n = 2)
Other	0.9 % (n = 1)

Table 17.2 Level of lesion in a subpopulation of N =110

Neurological level of injury	Percentage (number of cases)
C0	15.5 % (n =17)
C1	0.9 % (n =1)
C2	55.4 % (n =61)
C3	22.7 % (n =25)
C4	5.5 % (n =6)

Table 17.3 Distribution of the lesion severity classified by the ASIA impairment scale (AIS) in a subpopulation of N = 110

ASIA impairment scale (AIS)	Percentage (number of cases)
A	78.2 % (n = 86)
B	9.1 % (n = 10)
C	10.9 % (n = 12)
D	1.8 % (n = 2)

17.3 Pathophysiology

Different levels of an injury of the spinal cord results in different functional impairment patterns of the diaphragm, the intercostal muscles, the accessory respiratory muscles and the abdominal muscles [5] (Fig. 17.2).

Patients with an insufficient capability for coughing often have mucus retention. This increases the risk for atelectasis and pulmonary infections [6] and ultimately leads to a significantly higher mortality [7]. High tetraplegia is usually associated with the severest impairment of the respiratory function.

The paralysis of almost all respiratory muscles including the diaphragm leads to a significant loss of vital capacity and results in the dependency on partial or complete mechanical ventilation. In general, the rule applies that the more cranial the level of lesion is located, the more the respiratory pump is affected. Several factors contribute to this including:

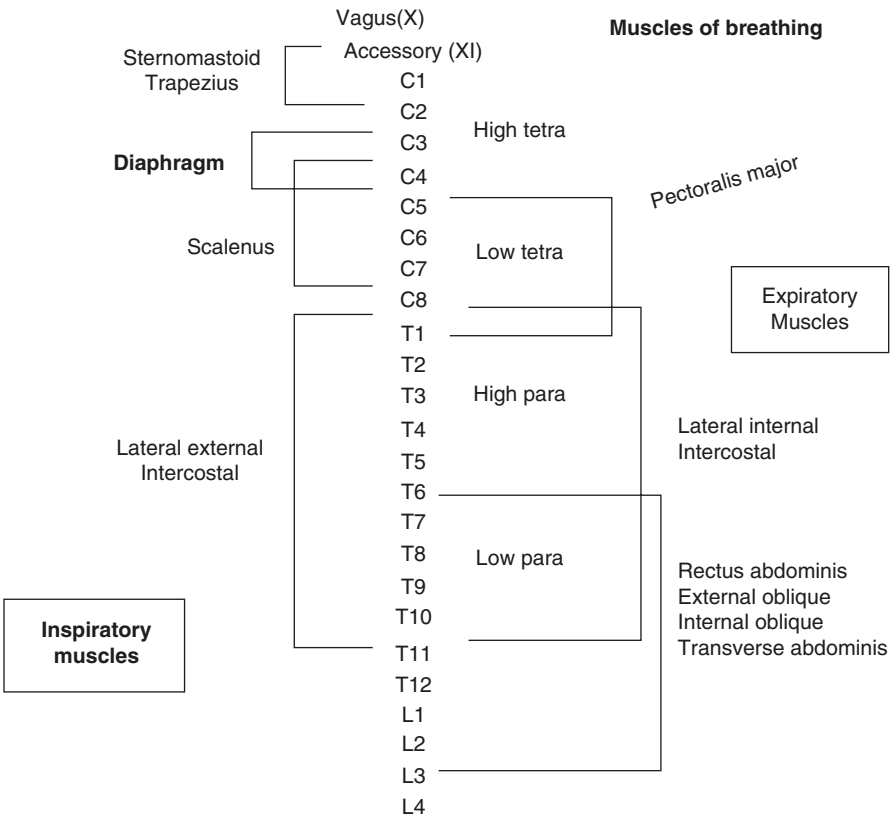

Fig. 17.2 Overview of the affected inspiratory and expiratory muscles in relation to the neurological level of lesion

1. The decreased strength of respiratory muscles
2. A reduced compliance of lungs and thoracic wall
3. A chronic central hypoventilation
4. Changes of the patency and reactivity of the airways
5. Dyssynergies concerning the muscles of the thorax and abdomen

Decreased Strength of Respiratory Muscles As a result of the weakness of inspiratory muscles, the vital capacity (VC), the tidal volume (TV) and the forced one-second capacity (FVC1) decrease in patients with high cervical SCI [8]. While patients try to maintain a sufficient minute volume, they automatically increase their respiratory rate.

The reduced strength of expiratory muscles leads to a decrease of the end-expiratory reserve volume and, as a consequence, to a rise of the residual capacity. This in turn decreases the vital capacity [9, 10]. Another result of the weakness of expiratory muscles is a limited ability to cough with the associated reduction in peak cough flow [9, 11]. With peak cough flow less than 270 l/min, efficient coughing is not possible [12, 13]. The measurement of peak cough flow with a peak-flow meter represents a simple and inexpensive method to objectively assess the ability for patients for sufficient coughing, which can be easily implemented into the clinical routine.

Reduced Compliance of Lungs and Thoracic Wall The lung and thorax compliance is worsening immediately after the lesion in tetraplegic patients caused by decrease of the vital capacity and changes of the surfactants due to respiration with low tidal volumes [14, 15]. Additionally, the reduced stability of the thorax due to partially or completely paralysed intercostal muscles leads to a paradoxical inspiration, which means that the thorax flattens during the inspiration [16, 17]. Stiffening of the thorax and potential spasticity of the intercostal muscles contribute to the decrease of compliance [18].

Chronic Central Hypoventilation The central control of respiration is affected in tetraplegic patients. The underlying mechanisms have not been entirely investigated. As far as we know, breathing effort, as a response to a hypercapnia, is decreased and correlates with the blood pressure fluctuations caused by the spinal lesion. Especially at night, breathing and sleep disorders may become more apparent and, in case of complementary drug therapy, partially enhanced by side effects of centrally acting medications (such as pain and antispastic medications) [19, 20].

Changes in the Patency and Reactivity of the Airways A bronchial hyperreactivity often occurs after cervical SCI and is significantly associated with decreased airway diameter and patency [21]. Hypoactivity of the disrupted sympathetic airway innervation, in addition to a parasympathetic hyperactivity, is assumed as a cause not only for the hyperreactivity but also for the increased production of bronchial secretions and bronchoconstriction [21, 22].

Dyssynergies of Muscles of the Thorax and Abdomen The interaction between abdominal and thoracic muscles is also impaired after high cervical SCI. The increased compliance of the abdomen as a consequence of the loss of voluntary innervation of abdominal muscles results in a caudal shift of the diaphragm. The weight of the intra-abdominal organs additionally contributes to a ventral and caudal displacement. Therefore, the vertical diaphragmatic effectiveness decreases, and patient transfers such as mobilisation in a wheelchair lead to a decrease of the tidal volume and accordingly, to a faster occurrence of dyspnoea [23, 24]. Thus, static and dynamic lung volumes are reduced as a direct consequence of the paralysis.

A long-term degradation of lung function is often reported [14, 25–28]. Additionally smoking, persistent wheezing, being overweight and the level of the lesion also have a negative impact both on the tidal volume in terms of significant reduction and lung function according to poor oxygenation [25, 26, 29].

17.4 Artificial Ventilation in the Acute Phase

17.4.1 Ventilation Modes

A limited or completely lost respiratory function can be adopted or assisted with an artificial respirator. Modern respirators offer at least two basic modes of operation, which are the mandatory and spontaneous ventilation mode. When in mandatory ventilation mode, the respirator controls and performs the breathing work completely or, in case of minimal residual respiratory function, in complemented mode. While working in complemented mode, important parameters (inspiration pressure, tidal volume and ventilation frequency) are monitored and, if necessary, adjusted by the respirator at any time.

The spontaneous ventilation mode allows the patient to either completely breathe on his own or to be supported by the respirator [30]. The two most important parameters in artificial ventilation are volume and pressure. With adaption of these two parameters, literally every available ventilation mode can be implemented [31]. Just as the discussion over the optimal ventilation mode continues, so does the debate over the optimal control variable. Volume-controlled ventilation (VCV) offers the safety of a preset tidal volume and minute ventilation but requires the clinician to appropriately set the inspiratory flow, flow waveform and inspiratory time. During VCV, airway pressure increases in response to reduced compliance or increased resistance and may increase the risk of ventilator-induced lung injuries. Pressure-controlled ventilation (PCV), by design, limits the maximum airway pressure delivered to the lung but may result in variable tidal and minute volume. According to current recommendations, the target tidal volume should range between 6 and 8 ml/kg body weight in patients with a normal body-mass index (BMI) [32].

Most studies comparing the effects of VCV and PCV were not well controlled or designed and offer little to our understanding of when and how to use each control variable in invasive ventilation [31]. Nevertheless, in SCI patients PCV seems to be more advantageous for prevention of atelectasis and for potential compensation of volume loss (e.g. phonation while ventilated with an unblocked cannula).

When choosing the ventilation mode for an individual patient, the clinicians have to keep in mind that a spinal cord-injured patient suffers from an impairment of the respiratory pump without a primary pulmonary disease. Patients with SCI and associated severe pulmonary diseases have to be treated additionally according to pneumological respiratory guidelines [31] including carefully selected medications and adapted ventilation modes.

17.4.2 Tidal Volumes

The aims of artificially assisted ventilation in persons with SCI are:

- Sufficient oxygenation with subjective well-being
- Prevention of forming atelectasis
- Enabling of phonation during ventilation

There are a few reports published about tidal volumes between 900 and 1000 ml (sometimes even higher) applied in patients with tetraplegia requiring invasive ventilation [33]. In case of a normal BMI, 10–15 ml/kg ideal body weight is recommended during the acute phase [34]. In the presence of atelectasis, a slow increase of 20 ml/kg ideal body weight with a maximal pressure of 30 cmH_2O is described in order to minimise the risk of a barotrauma [32, 35]. It was shown in a 10-year observational study that the risk for developing an atelectasis increases with lower tidal volumes [33]. As a consequence, it is recommended to apply higher tidal volumes for successful treatment of atelectasis while reducing the breathing frequency to avoid chronical hyperventilation [33].

On the basis of clinical experience with long-term ventilated tetraplegic patients with inserted unblocked tracheal cannula, six main advantages of using higher tidal volumes were stated [36]:

- Improvement of ability to speak
- Prevention of atelectasis
- Enablement of alternating ventilation volumes without developing hypoxemia
- Maintenance of pulmonary compliance
- Suppression of residual respiratory muscles activity due to low $paCO_2$ values
- Prevention of subjective dyspnoea during ventilation by achieving normal blood gas values

General observations of long-term ventilation with high tidal volumes show that the respiratory alkalosis associated with the hypocapnia can be completely renally compensated without pathological pH values. Theoretically possible negative effects of hypocapnia, e.g. reduced cerebral blood flow caused by vasoconstriction and thereby increased susceptibility for seizures, were not observed in the long-term course [37].

In principle, high tidal volumes with hyperventilation also offer the risk of potassium loss and increased osteoporosis by chronic hypocapnia [38]. The former has to be verified regularly and, if necessary, applied. Concerning osteoporosis it should

be noted that tetraplegia by itself is leading to an increased osteoporosis in the long-term course, to which many factors beside the hypocapnia contribute.

In conclusion, according to the literature, the following recommendations can be given with regard to invasive long-term ventilation of lung-healthy persons with tetraplegia:

1. Use of pressure-controlled ventilation modes with relatively high tidal volumes and reduced breathing frequency starting with 10–12 ml/kg ideal body weight in normal BMI depending on the clinical course (e.g. if atelectasis develop) can be applied. A maximal inspiratory ventilation pressure of 30 cmH_2O should not be exceeded. If necessary, tidal volumes of 15–20 ml/kg ideal body weight may be used.
2. Although general recommendations for parameters of ventilation such as inspiratory pressure or ventilation frequency exist, there is still the need to individually adapt these parameters to every patient. These adaptations may arise from thermal and circulatory dysregulations or due to chances in muscular or bronchial spasticity. They should be based on the results of a volumetric and – also in the non-clinical follow-up – capnometric assessment.
3. Using a non-blocked or non-cuffed tracheal cannula on an individual basis for as long as possible to improves phonation and prevents of tracheal ulcers.

17.5 Rehabilitation of Ventilated Patients During the Acute Phase

17.5.1 Communication and Mobilisation

Invasively ventilated patients with SCI should be provided with the possibility to speak during the very acute phase of injury during the stay in the intensive care (ICU) and intermediate care (IMCU) units. Apart from the advantage of better communication and the associated higher quality of life, the opportunity to speak creates a higher level of laryngeal awareness. This may help to improve oral ingestion and to prevent episodes of aspiration [39].

The inability to speak poses a considerable restriction on participating in everyday life for patients which are in need of permanent or partial ventilation [40]. If only minor or moderate swallowing disorders are present, loud and clear phonation during invasive ventilation is feasible and can be learned [41–43]. Phonation always depends on airflow through the glottis enabling the vocal cords to vibrate and produce tones. Unrestricted patients normally phonate during expiration [44]. In contrast, phonation in ventilated patients mainly occurs during inspiration, because the required airflow from the ventilator is generated during the inspiration, while expiration mainly proceeds passively [45].

Acute and long-term ventilated patients have a high risk of developing pneumonia [46], decubital ulcers [47] and deep vein thromboses [48]. Therefore, mobilisation of those patients is recommended as early as possible, even in IC and IMC units [49–51]. To achieve this early mobilisation, appropriate equipment and personal resources must be present in the form of:

- Physicians and therapists experienced in SCI and ventilation
- ICU/IMCU monitoring including capno- and spirometry
- Provision of patient-adapted technical assistive devices (e.g. respirators, wheelchairs, lifter systems)

17.5.2 Tracheostomy

In the context of acute care of tetraplegic patients, a tracheotomy is often required to enable sufficient respiration and secretion management. Tracheostomy also may be needed in case of prolonged ventilator dependency if typical problems associated with the use of oropharyngeal or nasopharyngeal tubes appear. A tracheotomy can be done either by dilatation percutaneously (PT) or surgically as an open tracheostomy (OT). Further advantages of a tracheostomy are the early reduction or suspension of analgosedation resulting in an alert and compliant patient who is able to participate in a SCI-specific therapy programme, consisting of mobilisation into the wheelchair, phonation, food intake during ventilation and weaning.

In general, a tracheotomy is recommended in tetraplegic patients with:

- Motor complete tetraplegia (AIS A and B) [52]
- Vital capacity ≤500 ml
- Injury Severity Score (ISS) >32
- PaO_2/FIO_2-ratio <300 for 3 days after initiation of ventilation [53]

Studies also demonstrated that an early tracheotomy (<10 days after the onset of paralysis) shortens both the duration of stay in an intensive care unit and the overall ventilation period (assuming that weaning was successful) [54]. With regard to complication rates of both techniques (PT and OT), there is inconsistent evidence [55, 56]. In the case of a permanently invasively ventilated patient, the current German Respiratory Society guideline "non-invasive and invasive ventilation" recommends stable medical care for outpatient ventilation and therefore the placement of an epithelial open tracheotomy [57]. Regardless of the used technique, PT can only be accepted for a short and successful weaning process in the ICU/IMCU or exceptionally in home mechanical ventilation due to the tendency to shrink and the risk of malposition of the cannula [57].

17.6 Weaning

Even for specialised centres, weaning of ventilated tetraplegic patients is a challenge for many reasons especially because of recurrent pulmonary infections [58]. Besides this, vegetative dysfunctions such as hypotonia, bradycardia, autonomic dysreflexia or hypothermia represent additional complications during the weaning process [59, 60]. Weaning in SCI patients is often prolonged and interrupted [61, 62]; therefore, the majority of the patients are ventilated via tracheotomy. The

length of this process ranges between 40 and 232 days. The rate of weaning failure is consistently reported to be in the range of 30 % [62].

17.6.1 Pathophysiology

The innervation and strength of the diaphragm muscle determines the vital capacity of the lungs [63, 64]. The higher the vital capacity, the better the weaning prognosis [65]. Therefore the weaning process should not be initiated when the vital capacity of a lung-healthy patient is below 1000 ml [66]. The aim during the weaning process is to systematically train the diaphragm muscle while avoiding excessive fatigue of the muscle. Disregard may lead to an extension of the weaning period or failure of the weaning process [67].

The diaphragm muscle is prone to a fast conversion from slow-fatiguing type I to fast-fatiguing type IIb fibres after paralysis. The training during the weaning reverts this paralysis-induced fibre transformation and leads to more slow-fatiguing muscle fibres [68–71].

17.6.2 Confounding Factors

From the clinical experience, weaning should not be started or must be interrupted when at least one of the following confounding factors is present:

- Pneumonia
- Septicaemia
- Constant fever >38.5 °C
- Complete paralysis of the diaphragm muscle
- Vital capacity <1000 ml
- Relevant autonomic dysreflexia
- Severe spasticity of relevant respiratory muscles
- Serious pressure sores
- Constant heart rate >140 bpm
- Constant breathing rate >35/min
- Metabolic acidosis
- Inadequate mental status
- Anaesthesia

17.6.3 Execution of the Weaning Process

Weaning should be started in a lying or reclined position (bed or wheelchair) during daytime (e.g. 8 a.m.–8 p.m.) in the ICU under the control of certain vital parameters. This includes breathing frequency, breathing (tidal) volume and values of carbon dioxide (capnography). During night-time recovery of all respiratory muscles should be ensured by correct settings of mandatory ventilation modes of the external respirator [66].

During the daytime, every hour should consist of a spontaneous breathing (training) part and a ventilator (recovery) part. In clearly defined steps of 5–10 min, the training sessions (up to 12) are slowly increased day by day until the patient is breathing spontaneously 12 h without any ventilator support. If the patient is stable during daytime, the night-time weaning can be initiated with increasing periods of spontaneous breathing, e.g. 1 hour per night.

The mentioned vital parameters including spirometry should be monitored and the weaning process interrupted, if confounding factors evolve. The application of a standardised protocol is recommended [15, 72, 73].

The supervision and adaption of the weaning process requires a highly trained staff to achieve a successful outcome. This knowledge is normally only present in specialised SCI centres. Therefore, the rapid transfer of patients in need of artificial ventilation from the ICU to SCI centres is recommended by SCI societies worldwide to ensure an adequate weaning procedure.

17.7 Mucus and Secretion Management

The liquefaction and loosening of bronchial secretions improves effective ventilation and the weaning regime. It avoids atelectasis and pneumonia in temporary as well as in long-term ventilation [74–76].

Efficient mucus and secretion management is achieved by:

- Hyperinflation of the lungs up to the maximum capacity before the evacuation of mucus
- Specific positioning of the upper body (e.g. 135° or kneeling position; Figs. 17.3 and 17.4)
- Assisted coughing (Figs. 17.5, 17.6 and 17.7)
- Deep inspiration by means of air stacking or glossopharyngeal respiration
- Insufflation with artificial respiration bag, an intermittent positive pressure volume device (IPPV) or with in-exsufflators (e.g. Cough assist®, Philips GmbH Respironics, Herrsching, Germany; Pegaso®, Dima Italia S.r.l. Bologna, Italy; Nippy-Clearway®, B&D Electromedical, Warwickshire, England), followed

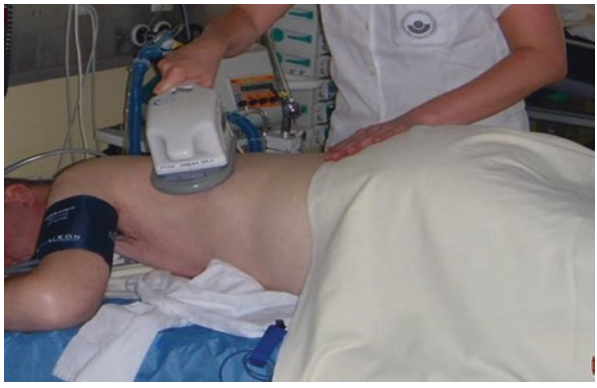

Fig. 17.3 Manual secretolysis bedside by using a vibrax massage device

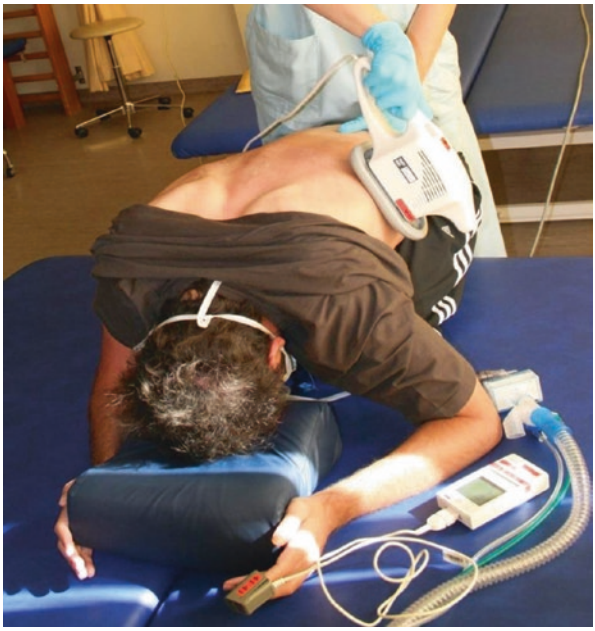

Fig. 17.4 Manual secretolysis during physiotherapy by using a vibrax massage device

Fig. 17.5 Chest compression made by one person

by manual cough assistance by means of dorso-cranial compression on the upper abdomen
- Inhalation with hyperosmolar saline
- Extra- or intracorporal chest vibration (e.g. Vibrax®, HEBRU-THERAPIEGERÄTE GmbH, Igersheim, Germany; Acapella®, MPV MEDICAL GmbH, Putzbrunn, Germany; Cornett®, R. Cegla GmbH & Co. KG, Montabaur, Germany; water bottle) (Figs. 17.3, 17.4, and 17.6)

Before initiating outpatient ventilation, the patient and the caregivers must be instructed and trained in the procedures of efficient secretion management.

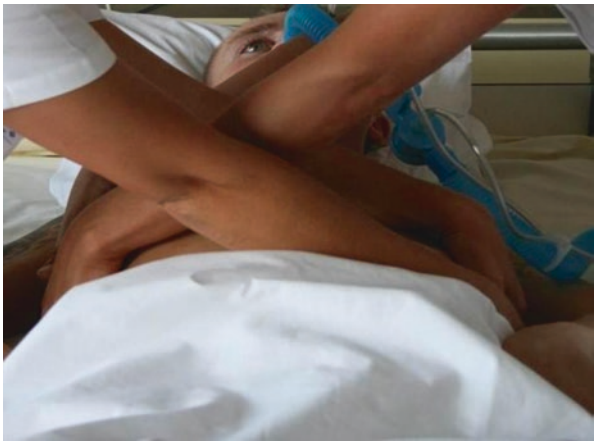

Fig. 17.6 Chest compression made by two persons in combination with an intermittent positive pressure-supported inspiration

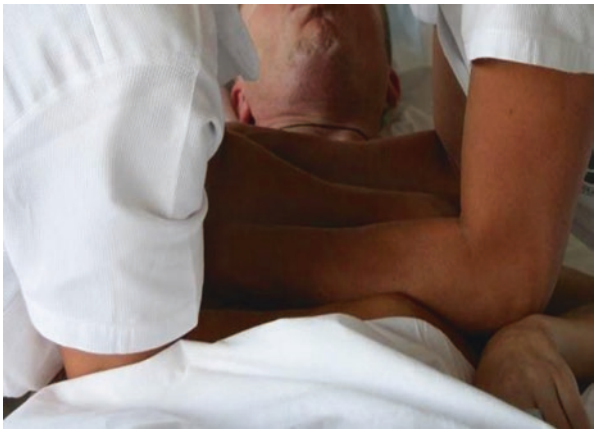

Fig. 17.7 Chest compression made by two persons during exhalation

Knowledge about the value of maximum inspiratory capacity and maximum peak cough flow is obligatory. Manually assisted coughing in combination with hyperinflation of the lungs should be performed in all patients with peak cough flow <270 l/min [77–79]. Cough assisting machines should be used in addition when hyperinflation and supported coughing fails [80–82]. Air-warming and air-moistening should be used regularly in invasively ventilated patients. Active (breathing gas humidifier) and passive (heat and moisture exchange filter) procedures are both reliable and convenient ways for dissolving mucus.

17.8 Long-Term Ventilation in the Chronic Phase

Objective information about the pattern of use of artificial ventilation in the chronic stage after SCI is rare. The following data from Germany may serve as a reference for western industrial countries [4] (Table 17.4):

Table 17.4 Modes of ventilation in chronic SCI ($N = 110$)

Period of ventilation	Percentage (number of cases)
24 h-MV	45.5 % ($n = 50$)
24 h-PNS	20.9 % ($n = 23$)
MV/spontaneously	17.3 % ($n = 19$)
MV/PNS	10.9 % ($n = 12$)
PNS/spontaneously	5.4 % ($n = 6$)

MV mechanical ventilation, *PNS* phrenic nerve stimulation

17.8.1 External Invasive Mechanical Ventilation in the Long-Term

In permanently ventilated patients, normally pressure-controlled modes are used (e.g. PCV), while volume-controlled modes are rarely applied (e.g. VCV). The longer a patient breathes spontaneously, the more often pressure-supported modes are used (e.g. PSV = pressure support ventilation), especially during the daytime. One reason for this might be the better ability to speak when using pressure-supported modes. Although having sufficient strength, pressure-controlled modes are often applied during the night-time to reduce the breathing effort of the patient [83].

17.8.2 Non-Invasive Ventilation (NIV)

The main area of NIV application is the ventilatory support of a SCI patient with signs of respiratory insufficiency during the night. Non-invasive ventilation may be used as a long-term therapy to compensate for the consequences of respiratory insufficiency including hypoventilation as well as obstructive and central apnoea [3]. Further diagnostic testing in the form of polysomnographic assessments is recommended, if one or more of the following conditions are present:

- Arterial $paCO_2 > 45$ mmHg during daytime
- Hypoventilation at night-time with constantly decreased oxygen saturation
- Constantly increased $paCO_2$ or $tcCO_2$ at night >55 mmHg (during 1 out of 10 min)
- Daytime sleepiness, especially in combination with hypertension
- Lack of concentration during the daytime

According to the German respiratory guidelines [31], the following contraindications must be excluded before initiating an NIV:

- Lack of cooperation
- Threat of aspiration (dysphagia)
- Upper airway obstructions
- Persisting and restraining mucus
- Pressure sores in the contact area of the mask [83]

When ventilator support is necessary, hospitalisation in a specialised centre is recommended, particularly in patients with more severe impairments of respiratory function. During this inpatient stay, individual and careful adaptions of interfaces, respirators and ventilation modes should be accomplished [3, 57]. The extent of nurse assistance while using mask and ventilator needs to be evaluated. If finger and/or hand functions are not sufficient and the patient is using a oral-nasal or full-face mask, any complication during ventilation (e.g. ventilator dysfunction, tube disconnection) could lead to a life-threatening situation, because an active intervention of the patient (e.g. removal of the mask) is not possible. Regarding NIV the compliance of tetraplegic patients compared to non-SCI patients is rather low. The main reasons for that are the impeded communication when using a mask and facial dysaesthesia resulting from mask pressure [83].

17.8.3 Phrenic Nerve Stimulators (PNS)

In the case of complete SCI above C3, phrenic nerve stimulators (PNS) represent a therapeutic alternative to permanent invasive ventilation. PNS was introduced in the mid-1980s for patients with severe respiratory insufficiency [84]. It has the advantage that the inhaled air is drawn into the lungs by the diaphragm under negative pressure, rather than being forced into the chest like in positive pressure ventilation (PPV). This is physiologically more accurate and comfortable for the patient. Currently there are two phrenic nerve stimulation systems commercially available, which have a CE or FDA approval for routine clinical use: the Atrostim Jukka® (Atrotech, Tampere, Finland) and the Avery System® (Avery Biomedical Devices Inc., New York, USA)

In both systems, electrodes are surgically implanted on both phrenic nerves in the mediastinum at the third to fourth intercostal space. Electrode leads are subcutaneously attached to a radio-frequency-operated receiver. The receiver is supplied with energy and receives the stimulation command from an induction coil placed on the skin area over the implant. No transcutaneous cables are needed for these systems.

Contraindications for the implantation of a PNS system are severe cognitive restrictions, e.g. as a consequence of a traumatic brain injury, a severe pre-existing condition of the heart and/or lung or an unfavourable prognosis in case of terminally ill patients. Intact lower moto neurons of both phrenic nerves and an intact diaphragm muscle are general prerequisites for a succesful use.

Possible complications during implantation are, besides the general risks, damages of the phrenic nerve (with consecutive dysfunction) and haemo- or pneumothorax.

Patients using a PNS are at much lower risk for upper airway infections including ventilator-associated pneumonia (VAP) due to the reduction in suctioning, elimination of external humidifier and ventilator circuits, and the potential, also temporary (e.g. with stoma buttons) removal of the tracheotomy tube in appropriate patients [85, 86]. Some studies showed significantly lower pulmonary complication rates and lower mortality rates. PNS provides some other benefits such as more

physiological breathing and speech patterns, ease of eating and drinking and improved sense of smell, which result in an increased quality of life [85–87]. The external components of PNS systems are relatively small compared to the bulky tubing and batteries of mechanical ventilators, and thereby they greatly improve the patient's mobility. The silent operation of a PNS enhances the patient's ability to participate in social and educational environments. Long-term observation studies showed that electrical motor thresholds do not change over time proving that the systems are suitable for chronic ventilation [88]. In contrast to external ventilators, running costs do not arise thus resulting in a financial compensation within a few years [85]. More than 70 % of all patients use the PNS for 24 hours per day. However, PNS 24 hours per day is recommended only for adults. For children and adolescents, a maximum of 12 hours per day is recommended, because sufficient bone development of the thorax must be ensured first.

17.8.4 Diaphragm Pacemaker (DP)

In more recent times, an alternative and more cost-efficient system for diaphragm pacing (DP) was introduced, which is the semi-invasive NeuRx® (Synapse Biomedical, Oberlin, OH, USA) system. In this system hook electrodes are laparoscopically inserted into the diaphragm muscle, and electrode cables are percutaneously connected to an external stimulator [88, 89]. The system has the advantage that only a minimally invasive implantation procedure needs to be performed with lower general surgical risks and faster recreation. However, pneumothorax is also one described complication during implantation. In chronic use diligent care and inspection of the site, where the percutaneous leads pass the skin, needs to be regularly performed to avoid infections and dislocations caused by third-party influences (e.g. mobilization in the wheelchair). Until now, sufficient data on associated infections are not available.

The (contra) indications of the DP system and the PNS are basically the same. At this point, it needs to be explicitly mentioned that although the DP system uses intramuscular electrodes, it is based on the stimulation of the phrenic nerves at the muscular endplates. Therefore, also in DP a sufficient number of lower moto neurons of both phrenic nerves need to be intact for successful application.

Permanent application over many years for 24 hours per day in patients with high SCI are described [90]. Some patients with preserved sensory functions complain about pain under stimulation, which is most likely be caused by the relatively strong stimulation currents [91].

With both systems, Magnetic Resonance Imaging (MRI) can cause nerve and muscle damage and therefore cannot be employed.

17.9 Long-Term Complications

Ventilated and non-ventilated patients with tetraplegia show significant differences in the distribution regarding the causes of complications at the time of readmission to the hospital. Table 17.5 summarises the results of an observational study involving 1.104 patients with the onset of tetraplegia minimum 2 years before the necessary

Table 17.5 Overview of long-term complications of non-ventilated and ventilated SCI patients

Type of complication	Percentage (number of cases) of non-ventilated patients ($N = 994$)	Percentage (number of cases) of ventilated patients ($N = 110$)
Urological complications	30.5 % ($n = 303$)	23.6 % ($n = 26$)
Decubitus ulcer	30.5 % ($n = 303$)	12.7 % ($n = 14$)
Pneumonia	8.5 % ($n = 84$)	41.8 % ($n = 46$)
Spasm	5.5 % ($n = 55$)	10 % ($n = 11$)
Fracture	2.7 % ($n = 27$)	2.7 % ($n = 3$)
Pain	11.0 % ($n = 109$)	2.7 % ($n = 3$)
Obstipation	8.3 % ($n = 83$)	2.7 % ($n = 3$)
Hypotonia	1.5 % ($n = 15$)	2.7 % ($n = 3$)
Others	1.5 % ($n = 15$)	0.9 % ($n = 1$)

complication treatment. Whereas pulmonary complications are most prevalent in ventilated patients, decubitus ulcers, obstipation and pain are the main reasons for re-hospitalisation in the non-ventilated population [4, 92]. Lower tidal volumes, positive pressure ventilation and the persistence of a tracheotomy represent risk factors for pulmonary infections. Remarkably, in ventilated patients, less severe decubitus ulcers occur. This may be a result of the 24 h per day care at home. Here, professional caregivers also take measures for minimising the risk of developing decubitus ulcers.

17.10 Mortality and Ageing

The general mortality rate of ventilated patients with tetraplegia is high (30 %) with an average survival time of 7.5 years after the onset of SCI. Due to the demographic developments, this rate is likely to continue to increase within coming years. In approx. 75 % of the cases, ventilated patients die because of typical SCI complications such as pneumonia and ileus [4, 85, 92] (Table 17.6).

It is remarkable that ventilated compared to non-ventilated patients with tetraplegia have a significant lower mortality rate during the primary rehabilitation stay (38 % after the first year after SCI). Most likely, this is explained by the permanent monitoring of vital parameters in the ICU or IMC, such that any complication can be detected and treated early. This is different after discharge, when ventilated patients have a higher mortality rate within the first 2 years (62 % in the first 2 years after discharge) compared to the non-ventilated population. However, if ventilated patients survive this vulnerable first 2 years at home, their health status seems to be more stable. This can be explained by the learning curve of the primary physician, nursing team and family members after discharge [92]. Remarkably, the suicide rate is relatively low (4 %) [93].

Long-term studies regarding phrenic nerve stimulated patients show a significantly lower mortality due to the lower rate of pulmonary infections (see Sect. 17.8.3.) [85, 88]. The average survival time after SCI ranges from 7 to 8 years for mechanically ventilated patients versus 8–10 years for PNS patients [85, 86, 94, 95] (Table 17.7).

Table 17.6 Causes of death of ventilated patients

Causes of death inpatient phase	Cause of death after discharge
50 % pneumonia	50 % pneumonia
20 % ileus	10 % decubitus ulcer
5 % thromboembolism	15 % bowel/urological complications
25 % not SCI related	2 % suicide
	23 % not SCI related

Table 17.7 Causes of death of patients with PNS vs. MV

Cause of death after discharge	
PNS	MV
30 % pneumonia	70 % pneumonia
15 % pressure sore	5 % pressure sore
17 % bowel/urological	13 % bowel/urological
38 % not SCI related	8 % not SCI related
0 % suicide	4 % suicide

17.11 Quality of Life (QoL)

Studies regarding QoL in ventilated SCI patients are rarely found. The few existing ones reported significant differences 1 year after SCI onset between the ventilator-user (VU) and non-ventilator-user (NVU) group.

The NVU group had significantly higher social integration scores than the VU group. The NVU group also had more positive perceived health status and a lower incidence of depression than the VU group [96]. No significant differences were determined between both groups for perceived current health status. Nonetheless, the literature suggests that perceptions of QoL improve as people live in the community for a longer period.

One study associated higher QoL scores in combination with suprapubic catheters, resulting less urological morbidity in comparison with intermittent catheterisation [97]. Furthermore it is reported that PNS patients score better in the field of social life than ventilated patients with positive pressure ventilation because the PNS system is more inconspicuous [86].

Conclusion

A high spinal cord injury above the fifth cervical level usually results in neurogenic respiratory failure. Nearly ten percent of all SCI patients need temporary or permanent ventilation as part of their initial treatment in the hospital and six percent from this group are in need of permanent artificial ventilation through a tracheotomy due to unsuccessful weaning attempts caused by failure of the respiratory muscles. Within the last 13 years, the number of long-term ventilated

patients has quadrupled. Additionally comorbidities such as reduced lung compliance, bronchial hyperreactivity, central dysregulations and higher age aggravate the ability to deliver adequate treatment. In the acute phase, early mobilisation, phonation despite ventilation and, if necessary, early tracheotomy are highly recommended and could minimise the risk of typical SCI associated complications such as pneumonia, thrombosis and bed-rest-related pressure sores. Simultaneously, an experienced team has to provide the selection of the most appropriate ventilator with a suitable mode, a continuous review of the vital parameters to detect weaning potential and, if possible, the initiation of the SCI-adapted weaning process. Even for specialised centres, weaning of ventilated tetraplegic patients is a challenge for many reasons especially because of recurrent pulmonary, vegetative dysfunctions such as hypotonia, bradycardia, autonomic dysreflexia or hypothermia.

During the chronic phase, the treatment is further adapted to the patient's status. Additionally, the patient is supported with assistive devices and a specialised, constantly present nursing team for the patient's integration into a barrier free home setting. If possible, at this stage, the implantation of a diaphragm stimulator could minimise the risk of suffering pneumonia, which is still the most common long-term complication. Studies on other long-term outcomes have shown that in the first 2 years after discharge, higher mortality rates are present, because of the individual learning curve of the multi-professional team. Subsequently, increasing survival rates accompanied with a sufficient quality of life were reported partly due to the continuous training for general practitioners, caregivers and family members.

For these reasons, SCI patients in need of artificial ventilation should be transferred to centres specialised in the treatment of SCI as early as possible after onset of the injury. After acute treatment and SCI-specific rehabilitation, they should be integrated into a SCI specific life-long care system in order to prevent life-threatening complications. Respective recommendations for ventilation in an outpatient setting have been published by SCI societies worldwide. These have led to the establishment of a generally high standard of care and treatment of SCI patients with ventilatory compromise.

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Medical Complications of Spinal Cord Injury: Bone, Metabolic, Pressure Ulcers, and Sexuality and Fertility

18

Steven Kirshblum and Jayne Donovan

Abstract

Spinal cord injury (SCI) results in significant bony, metabolic, skin, and sexual/fertility alterations. Rapid bone loss occurs after injury increasing the risk of fracture. In addition, individuals with SCI are also predisposed to extra-osseous bone formation, or heterotopic ossification, below the level of injury. Changes in basal metabolism and body composition after SCI often result in metabolic syndrome and increased risk of cardiovascular disease. Sensory and mobility impairments predispose individuals with SCI to pressure ulcer formation. Finally, SCI impacts both sexual function and fertility. Singularly or in combination, these changes result in significant morbidity and have the potential to negatively impact the quality of life in this population. For each of these complications, appropriate awareness, vigilance in prevention, and early intervention, when possible, are extremely important to improve the medical condition as well as the patient's overall quality of life.

18.1 Bone Changes After SCI

Evaluation and treatment of bone loss in patients after SCI is a clinical area that has emerged over time. Initially, when life expectancy after SCI was short, this metabolic consequence was not appreciated. However, with improvements in acute

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medical care resulting in greater survival, it has become clear that a unique process of bone loss occurs after SCI with excessive bone resorption, changes in bone architecture, and increased risk of fractures and related complications [1]. As with many other areas of SCI, bone health management is an example of a shift in emphasis of care from ensuring survival to minimizing long-term complications and maximizing quality of life.

18.1.1 Bone Loss After SCI

After SCI there is an uncoupling of the normal homeostatic mechanism responsible for maintaining bone. Immediately following injury, there is an initial increase in osteoclastic bone resorption and osteoblastic bone formation, however over the next several months osteoblast function slows resulting in net bone resorption and rapid bone loss [2]. This is reflected clinically by the onset of hypercalciuria.

Reports of the extent of bone loss in the acute period after SCI vary from 2 to 4 % per month [3, 4]. This is significantly higher than seen in other models of disuse osteoporosis, such as microgravity (0.25 % per week) and bed rest (0.1 % per week) [5, 6]. In addition to losses in bone mineral density (BMD) after SCI, structural changes occur in the geometry and distribution of bone mineral which may further impact bone strength. Edwards et al., using a validated subject-specific finite element modeling procedure to quantify changes at the proximal tibia after acute SCI, found strength reductions two times greater than reductions in BMD [4].

After SCI, rapid bone loss occurs below the level of injury and primarily at load-bearing sites [7, 8]. Accordingly, bone loss in the upper extremities is seen with tetraplegia but not paraplegia. Studies have reported BMD of the lumbar spine to be normal or increased in individuals with chronic SCI and hypothesized that this may occur secondary to increased spinal loads associated with a disproportionate amount of time sitting or differences in mechanical function of the spine compared to the limbs [9]. More recently, this has been challenged as a spurious finding secondary to the limitations of imaging with dual-energy x-ray absorptiometry (DXA) where the presence of osteophytes, vascular calcification, micro-compression fractures, and other skeletal abnormalities exaggerate BMD [10].

Bone loss is most rapid in the first 14 months after injury [7]. By 2–3 years, 25–50 % of BMD is lost in the lower extremities [8, 11, 12]. Whereas in the past bone loss after SCI was thought to stabilize after several years, subsequent studies support a continual loss of bone mass up to 3 % per year [7, 13, 14]. The magnitude of bone loss in a given skeletal region varies based upon the type of bone. Specifically, there is greater loss in areas rich in trabecular bone compared to cortical bone [3, 13]. Therefore, in long bones, greater loss occurs at the metaphysis compared to the diaphysis.

The etiology of bone loss after SCI remains incompletely understood but is likely multifactorial. Mechanical unloading is thought to play a major role. At a molecular level, it causes the upregulation of sclerostin, a Wnt signaling pathway antagonist produced by osteocytes that is a potent inhibitor of bone formation. Mechanical

unloading also leads to upregulation of receptor activator of nuclear factor kappa-B ligand (RANKL) and downregulation of osteoprotegerin (OPG) expression increasing osteoclast differentiation and activity. In addition, neural, hormonal, vascular, autoimmune, nutritional, and behavioral factors may also impact bone loss after SCI, but their relative contributions remain unclear [15]. Level of injury and health-related complications do not seem to influence the intensity of bone resorption [2]. Secondary causes of osteoporosis, such as thyroid disease, parathyroid disease, hypogonadism, renal disease, and chronic liver disease, have been shown to be present in approximately 30 % of patients with SCI and should also be considered [1].

18.1.2 Fractures

Fracture below the level of injury is a well-known complication of bone loss after SCI. The prevalence of fracture in the chronic SCI population is ~25–46 % [16–18]. Nevertheless, this is likely an underestimate as individuals with impaired sensation may not recognize the presence of fracture and thus may not seek medical attention. Fractures are relatively uncommon in the first years after SCI and then increase linearly with time; the mean time to first fracture is ~ 9 years [19]. The most common areas of fracture are at the knee (distal femur and the proximal tibia), followed by the distal tibia, femoral shaft, femoral neck, and humerus [16, 20].

Many factors have been shown to increase the risk of fracture after SCI including female gender, increased age, increased time post-injury, paraplegia, motor complete injuries, low body mass index, low knee-region BMD, and the use of medications including anticonvulsants, heparin, and opioids [18, 20–27]. The majority of fractures after SCI are fragility fractures, caused by injury that would be insufficient to fracture normal bone, in contrast to incident fractures, which are caused by injury sufficient to fracture normal bone. Most fractures occur while performing normal activities of daily living such as transfers, low-impact collisions, falls, or even stretching [17, 22, 28]. Torsional loading has been implicated as playing a major role.

Symptoms of acute fracture vary but can include fever, pain, swelling, increased spasticity, or autonomic dysreflexia (AD). Work-up with a standard x-ray is usually sufficient. For individuals who are ambulatory, management is similar to the non-SCI population. However, in individuals who do not use their lower extremities (LEs) for functional mobility, the main goals of treatment are to preserve pre-fracture function and allow for healing with satisfactory alignment while minimizing complications. Many times surgery, circumferential casting, and external fixation are not indicated because of low bone mass, recurrent bacteremia, and risk of skin breakdown and osteomyelitis [2, 29, 30]. Non-operative treatment using soft-padded splints such as a well-padded knee immobilizer for femoral supracondylar, femoral shaft, and proximal tibia fractures or a well-padded ankle immobilizer for distal tibia fractures is commonly recommended. Patients are allowed to sit after a few days, and ROM is initiated at 3–4 weeks. Weight bearing is often delayed for a longer period of time. Surgical intervention is generally recommended for

fractures that occur in the proximal femur; have rotational deformity, associated severe muscle spasms, and poor vascular supply; or will result in unacceptable functional or cosmetic outcomes.

Fracture-related complications after SCI are estimated to occur in over 50 % of cases [31]. Fracture nonunion occurs in 2–20 % of cases but is not clinically significant in individuals who do not bear weight in their LEs. Other complications such as contracture, skin breakdown, and deep vein thrombosis (DVT) can result secondary to relative immobility. Altogether fracture in this population can reduce functional independence, increase morbidity, and increase healthcare utilization and costs making the evaluation and treatment of bone loss after SCI a priority.

18.1.3 Diagnosing and Monitoring for Osteoporosis

The diagnosis and management of osteoporosis is best defined for postmenopausal women. In this population, DXA is considered the gold standard for diagnosing osteoporosis and is the most widely used assessment technique for determining treatment effectiveness. Using the World Health Organization (WHO) criteria, the diagnosis of osteoporosis among able-bodied postmenopausal women is made using DXA with an aerial BMD T score which is ≥2.5 standard deviations (SD) below the young adult mean [32]. For other able-bodied populations, including men under the age of 50 and premenopausal women, a Z score comparing an individual's BMD to age-matched peers is used. A Z score of ≤ −2 SD is used as rational for initiation of therapy.

In contrast to osteoporosis management for the general population, the practices among clinicians for screening, prevention, and treatment of bone loss after SCI are diverse. In 2009, Morse et al. found only 59 % of VA SCI practitioners had ordered a work-up for SCI-induced bone loss, and among these individuals, there was significant variability [33]. Since then, Craven et al. have published a decision guide for rehabilitation professionals on the identification and management of bone health issues for people with SCI [1]. Nevertheless there continues to be a lack of consensus on the best approach [34].

DXA has been suggested as a noninvasive and relatively safe method of identifying and monitoring bone loss in individuals with SCI. Nevertheless, as many patients with chronic SCI have Z scores ≤ −2 SD, this value taken alone is less meaningful in stratifying fracture risk compared to the general population. In addition, several logistical barriers have been identified in performing a DXA scan on individuals with limited mobility [35]. Finally, the standard sites of DXA measurement are not consistent with the most common sites of fracture after SCI. Hip BMD has been found to moderately correlate with distal femur BMD and is only marginally correlated with proximal tibia BMD [36]. Accordingly, the distal femur and proximal tibia have been proposed as sites for BMD measurements in patients with SCI and have been found to best predict fracture risk [21, 23, 24]. Several methods for measuring BMD at these sites have been established; nevertheless, the specific protocols are still not widely available [36, 37].

Craven et.al. suggest evaluation of BMD at the lumbar spine, hip, and knee BMD using DXA in persons with chronic SCI and establishing a diagnosis of osteoporosis based on a combination of BMD results (T or Z score) and fracture risk factors. The specific criteria they propose include hip or knee Z score ≤ -2.0 in premenopausal women and young men with three or more risk factors, hip or knee T score ≤ -2.5 in postmenopausal women or men over age 60, or history of fragility fracture with no identifiable etiology of osteoporosis other than SCI [1]. In addition to determining a Z or T score based on DXA, measurement values of BMD can be compared to a fracture threshold, value below which fragility fractures begin to occur, and a fracture breakpoint, value below which the majority of fractures occur [21]. At the knee the fracture threshold is ≤ 0.78 g/cm^2 [21] and the fracture breakpoint is <0.49 g/cm^2 [23]. Some clinicians follow BMD with DXA serially in individuals with SCI to monitor changes in bone loss and to assess effectiveness of treatment.

Peripheral quantitative computed tomography (pQCT) has also been suggested as an imaging technique to evaluate bone loss after SCI. In addition to assessing bone density, it can differentiate cortical from trabecular bone and quantify bone architecture. pQCT is currently used primarily as a research tool.

Biochemical markers of bone metabolism can supplement imaging in the assessment of bone health after SCI and may improve the ability to identify patients at risk of fracture and monitor response to therapy [2]. Biochemical markers have been shown to be reliable, noninvasive, and relatively cost-efficient for bone turnover assessment; however, there continues to be a lack of consensus regarding which biomarkers are best to monitor after SCI. Markers of bone formation include bone-specific alkaline phosphatase (BALP), osteocalcin (OC), N-terminal propeptide of type I collagen (PINP), and C-terminal propeptide of type I collagen (PICP), whereas markers of bone resorption include urinary free and total pyridinoline (Pyr), deoxypyridinoline (DPD) cross-links, type 1 collagen C-telopeptide (CTX), and N-telopeptide (NTX). Although not used regularly in clinical practice, several recent studies have proposed the potential role of biomarkers for fracture risk, including sclerostin and adiponectin, in this population [38, 39].

18.1.4 Prevention of Bone Loss

A recent review concluded that there is "overwhelming evidence that supports the importance of addressing bone health issues early after SCI" but recognized that significant variability in study designs makes interpretation of the literature regarding prevention and treatment options difficult [40]. Preventative education focused on informing patients of their increased risk and high-risk activities, regular assessment of functional abilities including transfer techniques and wheelchair skills, and retraining when necessary is a low risk and clinically feasible option [28]. Other options include the use of rehabilitation modalities and pharmacologic treatment.

Modalities that have been investigated for the prevention of bone loss after SCI include standing and walking, electrical stimulation (ES), functional electrical

stimulation (FES), and ultrasound. Studies are limited by low numbers of participants, inconsistency in duration and intensity, and significant variability in primary outcome measures. While some clinicians advocate for early use of ES to maintain bone, overall recent reviews have concluded that rehabilitation modalities do not prevent bone mass decline in the acute phase of SCI [40, 41].

Studies of pharmacologic prevention of bone loss in acute SCI have focused on the use of bisphosphonates that inhibit bone resorption by inhibiting osteoclast recruitment, reducing the osteoclast lifespan, and inhibiting osteoclast activity. Early studies demonstrated bisphosphonates could maintain bone in this population but included patients with less severe injury and were short in duration [42]. Since then, studies have shown mixed results. Taken together they show some evidence that bisphosphonates may reduce bone resorption but do not totally prevent BMD decline [43, 44]. A major limitation of these studies is the lack of evaluation of BMD at the knee. In a recent study by Bauman et al., zoledronic acid administered within 12 weeks of injury preserved BMD at the hip but failed to do so at the knee suggesting that more research is needed before recommending bisphosphonates universally after SCI for the prevention of bone loss [45].

18.1.5 Treatment of Osteoporosis

Treatment of bone loss after SCI includes addressing secondary causes of osteoporosis, lifestyle modifications, supplementation, rehabilitation interventions, and consideration of pharmacologic intervention. Craven et al. recommend counseling patients on the effects of smoking, excessive caffeine, and alcohol on bone health [1]. In patients with chronic SCI, after the rapid phase of bone resorption is complete, supplementation with calcium 1000 mg/day is recommended for patients with reduced BMD and no premorbid or post-SCI history of renal or bladder calculi [1]. As vitamin D deficiency is very common after SCI and can negatively impact bone health, levels should be assessed and corrected with supplementation [46]. Nonetheless, the effects of lifestyle modifications and supplementation on reducing bone loss and fracture risk have not been fully studied in this population.

Several trials have explored the role of rehabilitation modalities in the treatment of bone loss after SCI. However, there are no conclusive indications for most interventions with the exception of FES [41, 47]. In chronic SCI, FES intervention greater than 3 days/week of more than 3 months duration has shown to significantly increase in knee-region BMD, but effects are only maintained if FES is continued [48]. Limited availability of lower extremity FES cycle ergometry for home or longitudinal use may limit sustainability of this treatment outside of the research setting. Low-intensity, high-frequency vibration is a relatively new modality that may impact bone loss but has yet to be fully studied.

Bisphosphonates are the most commonly prescribed pharmacological treatment for bone loss after SCI. Studies to determine the efficacy of bisphosphonates in treating bone loss in chronic SCI have conflicting results leading to differences in clinical approach [1, 34]. Similarly, several recent systematic reviews on the use of

bisphosphonates for the treatment of bone loss after SCI have come to different conclusions [40, 41, 47, 49]. The effect of bisphosphonates in preventing fractures in this population has not been studied. There are several promising new treatments including denosumab, an antibody inhibitor of RANKL; sclerostin, an inhibitor of the conical Wnt signal pathway in bone; and teriparatide, a recombinant PTH 1–34, but more research is needed. It is probable that the best treatment for bone loss after SCI in the future will be a combination supplementation, rehabilitation modalities, and pharmacologic agents.

18.2 Heterotopic Ossification in SCI

Heterotopic ossification (HO) is the formation of extra-osseous lamellar bone in soft tissue surrounding peripheral joints below the level of SCI. Clinically significant HO that results in diminished range of motion (ROM) and interferes with function occurs in ~10–20 % of individuals with SCI, with up to 5–8 % progressing to joint ankylosis [50–52]. In SCI, HO most frequently develops around the hip (anteromedial aspect most commonly), followed by the knee, elbow, and shoulder, and rarely presents in the small joints of the hand and foot. Risk factors for HO following SCI include complete neurologic injury, male gender, older age (less frequently seen in children and adolescents), DVT, spasticity, and a nearby pressure injury (PI). Other factors including nicotine use, tracheostomy, and urinary tract infections have been implicated [53].

The pathogenesis underlying the development of HO after SCI is not completely understood, but it is most commonly believed that a combination of proprioceptive dysfunction related to central nervous system disruption, local inflammatory changes due to trauma, spasticity, immobilization hypercalcemia, and humoral factors may lead to the migration of mesenchymal osteoprogenitor cells into the joint space [54, 55]. Damage to the sympathetic tracts may also promote HO by increasing the local vascularity and blood perfusion around the joint. At least two processes have an important role in the development of HO after SCI: the activation of pluripotential mesenchymal cells in the soft tissue and the local production of bone morphogenic protein (BMP). Mesenchymal cells in muscle may switch their differentiation from fibroprogenitor to osteoprogenitor pathway under the influence of BMP and then proliferate into bone-forming cells. The specific factors involved in the activation of mesenchymal cells in muscle and local induction of BMP expression are still unknown. The histology of HO is similar to normotopic mature bone with well-developed cortical and trabecular structures. The bone has a high metabolic rate, adding new bone at more than three times the rate of normal bone [51].

18.2.1 Clinical Features of HO

HO may present with a fever, although is not always present. Several days later joint swelling may occur that limits ROM, and if the knee is involved, an effusion may

appear. Pain in the affected region may be present. HO most commonly develops between 3 and 12 weeks after injury with peak incidence at 2 months. Differential diagnosis for this clinical presentation includes a DVT, fracture of the LE, septic arthritis, and cellulitis. Since DVT and PI may coexist with HO, one should always consider a combination of disorders occurring at the same time.

The extent of tissue involvement by HO varies. In some patients, only a small amount of bone develops around the joint not causing joint dysfunction, while in others massive ossification can be found resulting in severe functional limitations or ankylosis of the joint.

Long-term complications of HO include loss of ability to sit secondary to reduced ROM, chronic pain, development of pressure ulcers, DVT, and increase in spasticity, and in severe cases, adjacent neurovascular structures may be compromised leading to distal extremity swelling and nerve entrapment. HO may also present several years after the initial SCI associated with a newly acquired PI, DVT, or fracture. The appearance of HO late after SCI is usually associated with a more benign course and preservation of joint function.

18.2.2 Diagnosis

Laboratory tests are sensitive but not specific markers for HO. Serum alkaline phosphatase (ALP) is a nonspecific marker, but often the earliest laboratory indicator of HO and precedes radiographic presentation, with elevations present a few weeks within HO initiation. Although ALP usually rises reflecting osteoblastic activity during the formation of HO, in some cases it is not elevated. ALP is also limited because of other causes for elevation, e.g., skeletal injuries, surgery, and abdominal issues post-SCI. Because levels do not correlate with the amount or degree of bone activity, they should not be used to judge maturity of the new bone or predict its recurrence. An elevation of serum creatine phosphokinase (CPK) may be a more reliable predictor of HO [56, 57]. While nonspecific markers of inflammation such as C-reactive protein (CRP) and the erythrocyte sedimentation rate (ESR) can be useful in following disease activity [58], with normalization of the CRP correlating with resolution of the inflammatory phase of HO, any cause of systemic inflammation may result in these elevations. Urinary excretion of hydroxyproline and collagen metabolites correlates with ALP levels and can also serve as indirect markers for the presence of HO.

Triple-phase bone scan (bone scintigraphy) is the most sensitive imaging study in diagnosing early HO and can detect disease activity before calcification becomes apparent on plain x-ray. Evidence of HO can be seen as early as 2–3 weeks after injury on the first two phases of the bone scan that demonstrate hyperemia and blood pooling, with the third phase showing positive uptake up to a few weeks later [59, 60]. Plain radiographs may lag behind another few weeks to demonstrate findings. The earliest radiographic finding is a soft tissue mass followed by mineralization of the osteoid lesion. It takes longer to see periarticular bone formation; therefore, standard x-rays are not sensitive for early diagnosis of HO. Ultrasonography

may be positive early with finding of an echogenic peripheral zone and echolucent center and has the advantage of being a relatively inexpensive examination without requiring radiation [61]. MRI, with increased T2 signal (edema) in muscles, fascia, and subcutaneous tissue, can be helpful in diagnosing HO acutely [62]. CT scan may be used to determine the volume of bone for planning surgical resection but is rarely used to make an early diagnosis. Bone scintigraphy is also the best method to determine the maturity of HO, with a serial decrease or a steady-state uptake ratio being a reliable indicator of maturity. The value of this test in preoperative evaluation is limited, however, due to frequent finding of considerable activity of HO even after a few years.

Several classifications for HO are available that are predominantly based on radiographic findings. The Brooker Classification describes the progression of the ossification on an anteroposterior radiograph and is only applied for HO around the hip [63]. Finerman and Stover describes five different grades for HO around the hip based on radiographic evaluation [64]. Garland and coworkers proposed a radiographic classification composed of five groups for preoperative grading based on the extent of bone formation in soft tissue. These included 1, minimal; 2, mild; 3, moderate; 4, severe; and 5, ankylosis [65]. This classification can be used for any location of HO. Mavrogenis et al. recommended a description based on the location of HO to better estimate prognosis [66].

On the basis of radiographic findings and clinical course, Garland proposed two classes of HO [65]. Class I patients have radiographic progression of HO and elevated serum ALP for 5–6 months with HO thereafter becoming inert. Class II is characterized by a radiographic progression of HO with a persistent activity on the bone scan for an extended period of time. Patients in class II are more likely to ultimately require surgery.

18.2.3 Prophylaxis and Treatment

Prophylaxis of HO in SCI has been studied using several agents including etidronate (20 mg/kg/day for 2 weeks, followed by 10 mg/kg/day for 10 weeks initiated 20–121 days post-injury), slow-release indomethacin (75 mg daily for 3 weeks within 5 weeks of injury), and rofecoxib, with less HO formation and less functional deficits as compared with placebo [52, 67–70]. Rofecoxib is no longer available due to its side effects. Warfarin may also be an effective agent by inhibiting the formation of osteocalcin [71]. Prophylaxis is not routinely prescribed because of the relatively low incidence of morbidity and the potential interference with bone healing postsurgery.

Treatment options include ROM with gentle stretching, bisphosphonates, nonsteroidal anti-inflammatory drugs (NSAIDs) if not contraindicated, as well as possible radiation therapy and surgical excision later in the course. There is debate as to whether ROM has an impact on the formation or worsening of HO once it is present. While animal models have shown that new bone formation may occur following aggressive ROM, stretching, and forceful manipulation, there is limited

documentation substantiating this relationship in the SCI population [72, 73]. Once HO is diagnosed, it is not recommended to perform an aggressive ROM program that can induce additional tissue microtrauma, possibly leading to an increased formation of HO [74]. Careful and gentle mobilization of the affected joints is however recommended to prevent further loss of ROM and does not appear to accelerate HO formation [75]. After the acute inflammatory period, ROM with gentle and sustained pressure to slowly increase or maintain range may be performed. Low-load prolonged stretching at end range may increase ROM without causing tissue damage with the goal to maintain ROM within a functional range. More frequent but shorter duration of range may be helpful. The application of ice may help reduce inflammation. If pain is encountered, tissue trauma may be occurring. The acute phase of HO is a relative contraindication for the use of FES [73].

Treatment with bisphosphonates has been shown to decrease the rate of new bone formation in patients with HO; however, it has no effect on bone, which has already been deposited. This drug blocks the late phase of bone formation, the stage of mineralization, preventing the conversion of amorphous calcium phosphate to hydroxyapatite. The prophylactic dosages were initially used for the treatment of HO, although other protocols using higher doses of etidronate for an extended period of time to prevent rebound formation of HO were later recommended. There is no definitive protocol however prospectively studied in a randomized trial. A current recommendation is for oral administration of etidronate 20 mg/kg/day for 6 months if the CPK level is elevated at the time of diagnosis or 20 mg/kg/day for 3 months, followed by 10 mg/kg/day for an additional 3 months if the initial CPK level is normal [76]. With this regimen, there is faster resolution of edema with less rebound formation after the medication is discontinued. If the initial CPK is elevated or CRP >8 mg/dl, some recommend the addition of an NSAIDs until the CRP < 2 or CPK normalizes [58].

The most common side effect of etidronate is gastrointestinal, including nausea and vomiting in 10–20 % of patients. Administering the medication in divided doses 1–2 h before meals is recommended. Clinical trials with newer-generation bisphosphonates are ongoing. Although iv administration of etidronate reportedly led to quicker resolution of edema with less rebound formation after the medication was discontinued [77], this formulation is no longer available. NSAIDs have been studied in the treatment of HO [52, 68], although often limited in use because of the gastrointestinal complications especially in the initial periods post-SCI.

Pulse low-intensity electromagnetic field therapy (PLIMF) utilizes magnetic fields to increase oxygen levels and decrease toxic by-products of inflammation by increasing local blood flow and has been shown to be effective in preventing HO post-SCI [78], although not frequently used clinically at this time. Radiation therapy in a variety of doses has been described for patients with early HO formation [79]. The long-term risks however have not been studied. Given the possibility of long-term complications, radiation treatment is usually not utilized as a primary treatment.

Surgical excision is reserved for patients with severely limited ROM that causes significant functional limitations in mobility or ADL or directly resulting medical complications, such as pressure ulcers. Surgical indications for removal of HO around the elbow and shoulder are for improvements in feeding, hygiene, and

dressing and for clinical evidence of progressive ulnar nerve compression [80, 81]. Most clinicians recommend waiting until after the ectopic bone is mature by bone scan which may take up to 12–18 months to occur, although early surgery has been described [81]. MRI or CT scan best determines preoperative localization of HO.

Various surgical approaches have been utilized for the resection of HO. Wedge resection is the most common procedure; however, it is frequently associated with a significant blood loss. Other complications include wound infection, neurologic or vascular injury, and recurrence of the HO. After resection, it is beneficial to start gentle ROM at 72 h postoperatively and wait 1–2 weeks until soft tissue swelling subsides until active physical therapy is commenced. Postop treatment includes NSAIDs for 6 weeks and/or etidronate (20 mg/kg/day) for 3–12 months and/or radiation [50, 82, 83]. While radiation decreases the degree of recurrence of HO, complications include delayed wound healing, osteonecrosis, and the risk of developing sarcoma. In a small study ($n = 7$), individuals who received pamidronate pre- and postsurgery for HO had no recurrence, offering some evidence that pamidronate can halt progression of HO after surgical resection [84]. While recurrence of HO after resection is common [50, 82, 85], the measure of success of the surgery is by the functional improvement, i.e., wheelchair sitting, grooming, hygiene, feeding, and mobility capabilities.

18.3 Metabolic Syndrome

As the mean survival rate of persons with SCI has increased and this population ages, they are susceptible to many of the same chronic conditions as able-bodied persons. Just as cardiovascular disease (CVD) is the leading cause of mortality in the general population, it is also the leading cause of mortality in individuals with chronic SCI [86, 87]. Moreover, persons with SCI have been shown to have a higher incidence and earlier onset of CVD compared to the general population [86].

Metabolic syndrome, a constellation of central obesity, dyslipidemia, hypertension, and insulin resistance, is associated with a pro-inflammatory and prothrombotic state that directly promotes CVD [88]. Accordingly, a diagnosis of metabolic syndrome has been used to identify individuals at high risk of CVD in the general population. A similar concept can be applied to individuals with SCI as they share many of the same risk factors for CVD disease. In fact, when compared to the able-bodied population, people with SCI are more likely to have oral carbohydrate intolerance, insulin resistance, and reduced high-density lipoprotein cholesterol [89]. Moreover, SCI itself may present additional risk for CVD secondary to significant changes in metabolic function and physical activity [90].

18.3.1 Changes in Energy Balance, Activity Level, and Body Composition After SCI

In humans, energy balance is regulated by the hypothalamus and represents the difference between energy intake and expenditure. While energy intake occurs simply

in the form of caloric consumption, total daily energy expenditure (TDEE) is comprised of three components: basal metabolism, thermic effect of activity (TEA), and minimally, the thermic effect of food. Fat-free lean mass (FFM) comprised of muscle, bone, and organ tissue is the major contributor to basal metabolism [91]. SCI impacts basal metabolism through disruption of the somatic nervous system leading to significant muscle atrophy below the level of injury. Additionally, with higher-level SCI, interruption of the autonomic nervous system creates dominance of the parasympathetic nervous system reducing whole body metabolic demands [92]. It is estimated that the basal metabolic rate after SCI is 14–27 % lower than controls [93].

The TEA, influenced by site and quantity of movement, is also reduced after SCI. The TEA produced by the upper extremities is significantly lower compared to the LEs. Furthermore, physical activity levels of persons with SCI are generally less than controls. Ultimately, secondary to changes in basal metabolism and TEA, TDEE after SCI is reduced up to 22 % when compared to controls [94].

Beyond the impact on daily metabolism, inactivity may be an independent risk factor for CVD in this population. Inactivity after SCI can result in marked cardiovascular deconditioning. Additionally, it has been shown to be associated with increased adiposity, abnormal glucose homeostasis, reduced high-density lipoprotein (HDL), and elevated low-density lipoprotein (LDL), triglycerides (TG), and total cholesterol [95, 96]. Ultimately, skeletal muscle atrophy, changes in body metabolism, and reduced activity levels after SCI lead to a considerable alteration of body composition with a decline in FFM and an increase in percentage of body fat mass [97].

18.3.2 Pathophysiology of Metabolic Syndrome

Adipose tissue accumulation is thought to be the primary contributor to the development of metabolic syndrome in the general population. Similarly, altered body composition after SCI has been suggested as a primary factor contributing to increased glucose intolerance, insulin resistance, dyslipidemia, and CVD in this population. In addition to serving as a medium to store energy, adipose tissue also secretes hormones, pro-inflammatory cytokines, and prothrombotic agents that contribute to metabolic syndrome and CVD.

Three adipokines, or hormones secreted by adipocytes, have been implicated in the formation of metabolic syndrome: leptin, adiponectin, and resistin. Leptin increases linearly with adipose tissue and activates areas in the paraventricular hypothalamus to suppress appetite and stimulate basal metabolism via the sympathetic nervous system [98]. Nevertheless, with excessive adipose tissue, the effects of leptin are suppressed suggestive of leptin resistance. Resistin functions to inhibit insulin-signaling mechanisms at the receptor level in hepatic tissue [99]. On the other hand, adiponectin appears to have a cardioprotective effect increasing glucose disposal and energy oxidation in the CNS and facilitating insulin in the periphery. However, adiponectin functions in a negative feedback loop with decreasing levels with increased adiposity [100].

Adipocytes also release pro-inflammatory cytokines, interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) that contribute to vascular endothelial cell injury. IL-6 potentiates its pro-inflammatory effect by stimulating the release of CRP from the liver [101]. It also exacerbates hyperglycemia by stimulating the release of corticosteroids from the adrenal cortex [102]. Similarly, TNF-α facilitates the synthesis of CRP and fibrinogen in the liver [101]. Finally, prothrombotic agents, plasminogen activator inhibitor (PAI-1), and thrombin-activatable fibrinolysis (TAFI) are released by adipocytes. Levels are directly related to volume of adipose tissue. Both PAI-1 and TAFI function to inhibit fibrinolysis and may promote CVD.

18.3.3 Abnormal Lipoprotein Profiles After SCI

Increased adipose tissue specifically leads to dyslipidemia through several mechanisms. First, with increased adipose tissue, adipocytes accelerate the release of non-esterified fatty acids that accumulate in the liver and increase TG concentrations. Secondary to increased presence of non-esterified fatty acids and TGs, the liver produces excessive amounts of very low (VLDL) and LDL and lower amounts of apolipoprotein A, the major protein of high-density lipoprotein cholesterol (HDL-c). Additionally, in this setting, HDL-c is catabolized at a higher rate.

Changes in lipid metabolism develop early after SCI and progress overtime. The major disruption seen in men after SCI is a profound reduction in HDL-c. Bauman et al. reported that in men with paraplegia, 63 % had HDL-c values < 40 mg/dL, 44 % had values < 35 mg/dL, and 19 % had values < 30 mg/dL [103]. Reduced HDL-c levels are associated with higher neurologic level of injury, motor complete injuries, and increased abdominal circumference [90, 104]. In contrast to men, premenopausal women have HDL-c levels similar to the general population [105]. Serum LDL, total cholesterol, and TG in men and women with SCI have also been reported to be similar to that of the general population [103].

18.3.4 Abnormal Glucose Homeostasis After SCI

Excess adipose tissue contributes to insulin resistance and hyperglycemia through several different mechanisms. To begin, it reduces passive glucose transport into the cell. It also leads to phosphorylation of insulin receptor substrates (IRS-1 and IRS-2) with downstream effects again inhibiting glucose transport in the cell. Finally, increased hepatic adipose tissue, or fatty liver, promotes enhanced gluconeogensis and hepatic glucose release leading to hyperglycemia. Individuals with SCI have been shown to have lower fasting glucose levels compared to controls [106, 107]. On the other hand, glucose intolerance, characterized by hyperinsulinemia in response to a glucose challenge, occurs more frequently after SCI than controls suggesting that peripheral insulin resistance is the major factor responsible for impaired glucose homeostasis in this population [90, 106]. In a cohort of men with SCI,

Bauman et al. demonstrated that fasting serum glucose was only diagnostic for DM in 5 % of participants, whereas DM was diagnosed in 17 % of participants after a 2 h glucose tolerance test and hyperinsulinemia was present in 34 % of participants [103]. Peak serum glucose is associated with increased total body percent fat, complete tetraplegia, older age, and male gender, whereas peak plasma insulin is associated with increased total body percent fat and male gender [108].

18.3.5 Hypertension as a Risk Factor for CVD After SCI

Increased adiposity is also directly related to hypertension. In the general population, up to 70 % of new-onset essential hypertension cases have been shown to be directly related to excess body fat [109]. As mentioned, adipocytes release pro-inflammatory agents that can cause direct injury to vascular endothelium and leptin that leads to increased sympathetic activity. In addition, increased adipose tissue can increase the renin-angiotensin-aldosterone and directly compress the kidneys leading to increased intrarenal pressure and sodium retention [110].

While historically, neurogenic hypotension with average blood pressure values below the general population was commonly noted after SCI, an increased prevalence of hypertension has been reported in persons chronic SCI. Studies in veterans with SCI have found hypertension to be present in 22–45 % of individuals [111, 112]. Individuals with paraplegia appear to be at greater risk for developing hypertension compared to individuals with tetraplegia [103].

18.3.6 Metabolic Syndrome and Identifying Risk Factors for CVD After SCI

Given the increased risk of CVD after SCI, comprehensive risk factor evaluation should be a major focus of care for this population. Moving beyond the general concept of metabolic syndrome as a constellation of central obesity, dyslipidemia, hypertension, and insulin resistance that increases risk of CVD, several groups have established strict criteria for diagnosing metabolic syndrome. One of the most commonly used criteria was established by the International Diabetes Federation and includes the presence of central obesity ($\geq$94 cm for men and $\geq$80 cm for women) plus any two of the following four factors: TG level $\geq$150 mg/dL or specific treatment for this lipid abnormality, reduced HDL cholesterol (<40 mg/dL in males and <50 mg/dL in females or specific treatment for this lipid abnormality), raised blood pressure with systolic BP $\geq$130 or diastolic BP $\geq$85 mmHg or treatment of previously diagnosed hypertension, or raised fasting plasma glucose $\geq$100 mg/dL or previously diagnosed type 2 diabetes [113].

Using criteria for the general population, Nash et al. found that 34 % of individuals with SCI had metabolic syndrome [114]. Nevertheless, it is likely that general metabolic syndrome criteria or other common screening tools for CVD risk do not fully capture the changes in body composition, lipid profiles, glucose homeostasis,

and blood pressure after SCI. Therefore, modifications have been suggested for this specific population [115, 116]. Specifically, the anthropometric measures of adiposity commonly used in the general population are less meaningful after SCI. Waist circumference may be expanded to due to abdominal muscle paralysis. It also does not fully capture the changes in body composition that occur below the level of injury. Similarly, body mass index, which evaluates a person's weight relative to his or her height squared, does not consider differences in body composition. If fact, men with SCI have been shown to have on average 13 % greater adiposity per unit of BMI compared to controls [97]. If using BMI for individuals with SCI, it is likely that the true cutoff for obesity is closer to 20–22 kg/m^2 compared to 30 kg/m^2 for the general population [117]. Although not as easily accessible in a clinical situation, DEXA has been suggested as an alternative to assessing body composition after SCI [115].

It is also important to recognize that fasting glucose levels after SCI are commonly within the normal range despite impaired glucose tolerance and/or hyperinsulinemia. Therefore, screening of patients with a 2 h glucose tolerance test is recommended. Alternately, as glycosylated hemoglobin (HbA1c) levels above 6.0 % have been shown to correlate with impaired glucose tolerance, this test may also be considered for routine screening [118].

18.3.7 Treatment of Metabolic Syndrome

As change in body composition is the underlying etiology of metabolic syndrome after SCI, diet and exercise interventions are considered the cornerstones of treatment. Although individuals with SCI consume fewer kilocalories than the general population, they have been shown to consume levels of fat that exceed recommendations and likely still have a daily calorie surplus due to the significant reduction in energy expenditure [119, 120]. While there are no clear guidelines regarding nutritional recommendations specifically for individuals with SCI with glucose intolerance, dyslipidemia, and CVD, a routine nutrition assessment and education should be provided [121]. General recommendations include increasing intake of fruits, vegetables, fiber, and protein and reducing overall fat consumption. Dietary counseling in this population has been shown to improve lipid profiles, but more studies are needed to better understand the effects of dietary modification on the other elements of metabolic syndrome [122]. Consultation with a registered dietitian should be considered as an individualized diet considering patient preferences, environmental/social barriers, and physical limitations may enhance compliance [123].

Regular exercise after SCI improves cardiovascular fitness and glucose homeostasis [124]. Benefits in these areas can be seen even with minor changes in body composition. In a recent review, neuromuscular electrical stimulation or FES exercising the paralytic LEs were found to improve glucose metabolism with enhancement of insulin sensitivity being the major factor following training, although the effect on lipid profile is unclear and warrants further investigation [125]. Alternatively, several studies report positive effect on lipoprotein profiles, specifically raising HDL-c, with upper extremity ergometry [126, 127].

There is no consensus on the optimal exercise type, intensity, or duration after SCI, but there appears to be a minimal threshold to achieve cardiovascular health benefits. At a minimum, moderate intensity exercise performed 20–60 min/day for at least 3 days per week is recommended. Upper extremity ergometry may be a good option for many individuals with SCI due to its relatively low cost and ease of use in the home. While some concerns have been raised with repetitive upper extremity use with ergometry exacerbating pain and dysfunction secondary to shoulder overuse, initial investigation did not find an increase in shoulder pain after a 12-week program [128]. Increased costs and reduced availability of lower extremity FES and body weight-supported treadmill training may limit the generalizability of these exercise options to all individuals with SCI [129].

Medical clearance and supervised exercise should be considered in certain cases. A recent evidence-based consensus recommend individuals less than 6 months post-SCI, persons with established AD, persons who experience resting or exertional hypotension, and persons with recurrent or recent musculoskeletal injury that is worsened by physical activity receive medical clearance before initiating an independent exercise program [130]. Evaluation and follow-up with a physical therapist may help optimize physical activity participation and development of a customized home exercise program [131].

If the above lifestyle changes are not sufficient in improving glucose intolerance, lipid profile alterations, or blood pressure changes after SCI, pharmacologic intervention should be considered. Guidelines for the able-bodied population can be used to direct management with a few caveats for individuals with SCI. Treatment of diabetes in this population does not differ from able-bodied individuals except that individuals at risk of recurrent infections or hospitalizations may be more effectively managed with an insulin regimen [132]. For individuals with impaired glucose tolerance, metformin is considered the first-line pharmacologic treatment secondary to its reduced risks of hypoglycemia and water retention and cost-effectiveness. The side effects that accompany other glycemic-lowering therapies make them less attractive options for individuals with SCI.

For lipid alterations, it has been suggested that greater emphasis be placed on increasing HDL-c for individuals with SCI [90]. This can be accomplished with the use of niacin, a broad-spectrum medication that reduces all lipids and is the most effective agent for increasing HDL-c levels. The extended release version of this medication administered with a prostaglandin antagonist (e.g., 325 mg acetylsalicylic acid) and gradual dose titration reduces cutaneous flushing and improves tolerance. Nash et al. studied the effect of niacin in individuals with SCI and low HDL-c levels and found the medication to increase HDL-c levels by 24.5 %, reduce LDL and TC levels, and be safe and well tolerated in this population [133]. Nevertheless, as the use of niacin in the general population has decreased, the frequency of actual use in individuals with SCI at this time is unclear. Statins may also be considered for treatment of lipid alterations in individuals with SCI, but patients should be closely monitored for development of myalgias, which may impact daily function [44]. The safety, tolerance, and effectiveness of statin treatment specifically in SCI have not been studied to date.

18.4 Pressure Injuries (PI)

Pressure injuries are one of the most common and serious complications of SCI, acutely after injury and through the patients' lifetime. Up to 80 % of persons with SCI will at some time develop a PI [134–136]. During the acute stage after injury, approximately one-third of patients develop a PI, although the incidence may be lower for patients cared for at specialized SCI centers [137–140]. Diseases of the skin, including PIs, are the second most common cause of rehospitalization of persons with chronic SCI, with persons having ASIA Impairment Scale (AIS) A, B, or C paraplegia more likely to be hospitalized than those with any level of tetraplegia or AIS D paraplegia [141].

Pressure injuries can have a profound consequence on the patients' daily activities and quality of life as well as significant direct economic costs that include the medical treatment, attendant and skilled care, surgical costs (if required), and long-term hospitalization. It is estimated that PIs may account for approximately one-fourth of the total cost of care for individuals with SCI. PIs also have indirect costs including the loss of income, productivity, independence, self-esteem, and sense of self-worth. The National Pressure Ulcer Advisory Panel (NPUAP) revised the terminology of "pressure ulcer" to "pressure injury" in April 2016 [142], and this term will therefore be used in section.

18.4.1 Pathophysiology

A pressure injury is localized damage to the skin and/or underlying soft tissue usually over a bony prominence or related to a medical or other device. The injury can present as intact skin or an open ulcer and may be painful. The injury occurs as a result of intense and/or prolonged pressure or pressure in combination with shear [142, 143]. There is an inverse relationship between the amount of pressure and the duration of the pressure necessary to cause ulceration; intense pressure applied for a short duration can be as damaging as lower-intensity pressure for extended periods. When pressure is placed on a body surface, the greatest pressure is to the tissues overlying the bone, with muscle being more sensitive to the effects of pressure than skin. Shear, the application of force tangential to the skin surface, occurs when the skin remains stationary and the underlying tissue shifts. Shear can result from varied activities, for example, sliding rather than lifting during transfers.

There have been many risk factors studied for the development of PIs that include demographic and psychosocial variables with some inconsistencies in their findings [144]. During the acute rehabilitation phase, the presence of a PI on admission and possibly a lower functional independance measure (FIM) score are the greatest risk factors for developing a new PI during the hospitalization [138, 140]. Overall, longer duration of SCI and having a previous PI are significant risk factors for developing future ulcers. Other variables associated include male gender, use of tobacco and alcohol, and poor nutrition. Medical comorbidities, including cardiac disease, diabetes mellitus, vascular disease, immune deficiencies, collagen vascular

diseases, malignancies, psychosis, and pulmonary disease are also factors associated with PI development and may contribute to poor wound healing.

Long-standing ulcers (20 years or more) can, although rarely (<0.5 %), develop Marjolin's ulcers, a type of squamous cell carcinoma. Biopsy can identify the carcinoma that is suspected clinically with pain, increasing discharge, verrucous hyperplasia, and bleeding [145].

18.4.2 Staging/Grading/Location of Pressure Injury

Although there are a number of staging classifications proposed, the most commonly used is the NPUAP classification (Table 18.1). As mentioned in April 2016, there were revisions of the staging that include the following [142]:

1. The term *pressure injury* replaced *pressure ulcer*. This change was felt to more accurately describe pressure injuries to both intact and ulcerated skin. In the previous staging system, stage 1 and deep tissue injury described injured intact skin, while the other stages described open ulcers. This reportedly led to confusion because the definitions for each of the stages referred to the injuries as *pressure ulcers*.
2. Arabic numbers are now used in the names of the stages instead of Roman numerals.
3. The term *suspected* has been removed from the deep tissue injury diagnostic label.
4. Additional pressure injury definitions agreed upon at the meeting included medical device-related pressure injury and mucosal membrane pressure injury.

18.4.3 Pressure Injury Prevention

A comprehensive educational program for SCI patients and their family/caregivers is essential, including information on etiology, risk factors, proper positioning, equipment (e.g., cushions), complications, and principles of wound prevention, skin care, treatment, and when to seek medical attention. Prevention recommendations include examining the skin over bony prominences at least daily with the use of a mirror as needed, shifting body weight in bed and wheelchair on a regular basis, keeping the skin clean and dry if there is incontinence, having an individually prescribed wheelchair and pressure redistribution cushion or power tilt/recline mechanism, ensuring all equipment is maintained and functioning properly, nutritionally complete diet and maintaining appropriate body weight, stopping smoking, and limiting alcohol intake [134, 146].

Since pressure injuries occur over bony prominences, the site of injury development depends upon the position. When sitting, the ischial tuberosities (ITs) are at greatest risk; while in side lying, the greater trochanters become at risk; and in the supine position, the sacrum, heels, and occiput (especially in infants) are at risk for

Table 18.1 National Pressure Ulcer Advisory Panel's (NPUAP) terminology [142]

Stage	Description
Stage 1	*Non-blanchable erythema of intact skin* Intact skin with a localized area of non-blanchable erythema, which may appear differently in darkly pigmented skin. Presence of blanchable erythema or changes in sensation, temperature, or firmness may precede visual changes. Color changes do not include purple or maroon discoloration; these may indicate deep tissue pressure injury
Stage 2	*Partial-thickness skin loss with exposed dermis* Partial-thickness loss of skin with exposed dermis. The wound bed is viable, pink or red, and moist and may also present as an intact or ruptured serum-filled blister. Adipose (fat) is not visible and deeper tissues are not visible. Granulation tissue, slough, and eschar are not present. These injuries commonly result from adverse microclimate and shear in the skin over the pelvis and shear in the heel. This stage should not be used to describe moisture-associated skin damage (MASD) including incontinence-associated dermatitis (IAD), intertriginous dermatitis (ITD), medical adhesive-related skin injury (MARSI), or traumatic wounds (skin tears, burns, abrasions)
Stage 3	*Full-thickness skin loss* Full-thickness loss of skin, in which adipose (fat) is visible in the ulcer and granulation tissue, and epibole (rolled wound edges) are often present. Slough and/or eschar may be visible. The depth of tissue damage varies by anatomical location; areas of significant adiposity can develop deep wounds. Undermining and tunneling may occur. Fascia, muscle, tendon, ligament, cartilage, and/or bone are not exposed. If slough or eschar obscures the extent of tissue loss, this is an unstageable pressure injury
Stage 4	*Full-thickness skin and tissue loss* Full-thickness skin and tissue loss with exposed or directly palpable fascia, muscle, tendon, ligament, cartilage, or bone in the ulcer. Slough and/or eschar may be visible. Epibole (rolled edges), undermining, and/or tunneling often occur. Depth varies by anatomical location. If slough or eschar obscures the extent of tissue loss, this is an unstageable pressure injury
Unstageable	*Obscured full-thickness skin and tissue loss* Full-thickness skin and tissue loss in which the extent of tissue damage within the ulcer cannot be confirmed because it is obscured by slough or eschar. If slough or eschar is removed, a stage 3 or stage 4 pressure injury will be revealed. Stable eschar (i.e., dry, adherent, intact without erythema or fluctuance) on an ischemic limb or the heel(s) should not be removed
Deep tissue injury	*Persistent non-blanchable deep red, maroon, or purple discoloration* Intact or non-intact skin with localized area of persistent non-blanchable deep red, maroon, purple discoloration or epidermal separation revealing a dark wound bed or blood-filled blister. Pain and temperature change often precede skin color changes. Discoloration may appear differently in darkly pigmented skin. This injury results from intense and/or prolonged pressure and shear forces at the bone-muscle interface. The wound may evolve rapidly to reveal the actual extent of tissue injury or may resolve without tissue loss. If necrotic tissue, subcutaneous tissue, granulation tissue, fascia, muscle, or other underlying structures are visible, this indicates a full-thickness pressure injury (unstageable, stage 3 or stage 4). Do not use deep tissue pressure injury (DTPI) to describe vascular, traumatic, neuropathic, or dermatologic conditions

(continued)

Table 18.1 (continued)

Stage	Description
Medical device-related pressure injury	*This describes an etiology* Medical device-related pressure injuries result from the use of devices designed and applied for diagnostic or therapeutic purposes. The resultant pressure injury generally conforms to the pattern or shape of the device. The injury should be staged using the staging system
Mucosal membrane pressure injury	Mucosal membrane pressure injury is found on mucous membranes with a history of a medical device in use at the location of the injury. Due to the anatomy of the tissue, these injuries cannot be staged

PI development. Accordingly, the most common sites of PIs after SCI change based on the amount of time spent in a given position. Acutely after injury, the most common sites are the sacrum, followed by the heels and ischium. At 1 year, the most common sites are the sacrum, ischium, heels, and trochanters and, at year two post-injury, the ischium, sacrum, and trochanters. When in bed, an appropriate mattress should be sought. Pillows can be used to provide additional padding or provide pressure reduction over bony prominences. Most commonly prescribed early after injury is a turn frequency in bed every 2 h. Once discharged, it is common to extend the 2 h turn schedule although there is no documented protocol for this. The prone position has a large surface area of low pressure and is recommended in the chronic patients as tolerated.

Weight shifting, redistributing the pressure off of the IT to other areas to allow for reperfusion of the ischial areas, is extremely important when the patient is seated in the wheelchair and can be performed by the patient via a number of techniques including an anterior, lateral, or push-up weight shift. If the patient is unable to perform their own weight shift, a caregiver can assist or tilt the chair posteriorly so that the patient's weight is no longer on their IT.

While there is no absolute regarding the frequency and duration required for weight shifting while in the wheelchair, it is recommended that weight shifts be performed every ~15 min for >2 min to allow for adequate tissue reperfusion [147–149]. A weight shift in a tilt-in-space wheelchair should be >35° when combined with recline at 100°, or >25° when combined with recline at 120° [150]. This degree of tilt does not seem to increase pressure significantly over the sacrum [149]. When performing a tilt weight shift without any recline mechanism, a minimum of 45° is required for adequate pressure distribution [151].

Cushion selection is extremely important. No one cushion is suitable for all individuals with SCI, and prescription should be based on a combination of pressure mapping results, clinical knowledge of the prescriber, and patient preferences.

18.4.4 Treatment

The general principles of PI treatment are to relieve pressure; eliminate reversible underlying predisposing conditions; avoid friction, shear, and tissue maceration; keep

Table 18.2 Treatment principles

1. Assess and document wound (size, stage, wound bed appearance, wound edges, exudates, necrosis, odor, signs of infection, surrounding skin, undermining, sinus formation, tunneling, and degree of granulation tissue epithelialization)
2. Eliminate direct pressure over the pressure injury through positioning techniques and appropriate support surfaces. Limit time in chair if pressure injury is on the ischial tuberosities
3. Observe and document wound healing progress
4. Avoid antiseptics (povidone-iodine, H_2O_2, etc.) and cleansers with nontoxic dilutions
5. Keep periwound skin dry, control exudates, and eliminate dead space
6. Use dressings that keep pressure injury bed moist to allow for optimal cell migration, proliferation, and revascularization
7. Clean wound at every dressing change using minimal mechanical force
8. Create optimum wound environment by using modern dressings (hydrocolloids, hydrogels, foams, alginates, soft silicone) rather than gauze
9. Consider adjunctive therapies (i.e., electrical stimulation, negative-pressure wound therapy, etc.) to enhance healing for appropriate wounds
10. Consider a 2-week trial of topical antibiotics (neomycin, bacitracin, or polymyxin B) for clean, nonhealing injuries
11. Consider an infection if nonhealing wound (see below), and if so, manage with wound cleansing, systemic antibiotics, and debridement after diagnosis is made
12. Ensure adequate nutritional intake
13. Remove necrotic tissue by techniques that may include mechanical, autolytic (applying a moisture-retentive dressings, such as a hydrocolloid, or the use of hydrogels to moisturize the devitalized tissue), enzymatic (e.g., use of collagenase), biologic (use of sterilized eggs of *Lucilia sericata* commonly known as *maggot therapy*), pulsatile high-pressure lavage, or conservative sharp or surgical debridement

the wound bed moist; manage excessive drainage; and debride devitalized tissue [134, 152] (Table 18.2). In general, stage 1 and 2 PIs are usually treated with local care nonsurgically. Stage 3 and 4 PIs, because of their high rate of recurrence as well as the long duration necessary for wound closure, often require surgical intervention. Involvement of a wound care team early after a pressure ulcer (especially grade 3 and 4) has developed is important.

Silver, available in multiple forms (gel, cream of foam), is a nonselective broad-spectrum topical agent that covers gram-positive and gram-negative microorganisms in the management of colonized and locally infected wounds [153]. Silver-impregnated dressings are contraindicated in neonates, in pregnancy, in patients with significant renal or hepatic impairment, and in those with sensitivity to sulfonamides or large open wounds [154].

Systemic antibiotics are generally only warranted when there is bacteremia, sepsis, advancing cellulitis, or osteomyelitis. Swab cultures are not useful in determining the presence of infection of PIs and only reflect the bacteria on the surface of the ulcer. Tissue biopsy can determine if there are bacteria within the tissue, and if the bacterial count is greater than 10^5, wound healing may be impaired. Advancing cellulitis is indicative of invasive tissue infection and must be treated with appropriate antibiotics.

Approximately 25 % of nonhealing PIs have underlying osteomyelitis, and this should be ruled out if there is reasonable suspicion. Bone biopsy remains the definitive method to diagnose osteomyelitis and identifies the organism, although surgeons are often reluctant to perform this unless there are other compelling indications for surgery. The most common organisms isolated from PIs are *Proteus mirabilis*, group D streptococci, *E. coli*, *Staphylococcus*, *Pseudomonas* species, and *Corynebacterium* organisms. Conventional bone scan is more sensitive for osteomyelitis than plain films, although specificity is approximately 50 % because of difficulty differentiating soft tissue infection from bone infection. Indium leukocyte scans improve the sensitivity and specificity. MRI has greater sensitivity and specificity. Treatment of osteomyelitis includes appropriate antibiotics for 6–12 weeks.

While there are numerous adjunctive therapies, only electrical stimulation has merited recommendation and can be considered for clean stage 2, 3, and 4 injuries that are unresponsive to conventional therapy. Electrical stimulation accelerates the healing rate of ulcers when combined with standard wound management [144]. The therapeutic efficacy of hyperbaric oxygen; infrared, ultraviolet, and low-energy laser irradiation; and ultrasonography has not been sufficiently established for recommendation. Ultrasound/ultraviolet C can be considered as an adjunct treatment when PIs are not healing with standard wound care post-SCI.

Platelet-derived growth factors (PDGF) can be applied directly to the wound surface to promote growth of skin, soft tissue, and blood vessels. Becaplermin (Regranex), a commercially prepared biotechnology product with recombinant PDGF as the active ingredient, in conjunction with good wound care, is efficacious in accelerating wound closure of chronic diabetic ulcers [155, 156]. This product, however, carries a warning indicating that patients who use in excess of three tubes may experience increased mortality due to malignancy.

Negative-pressure wound therapy (NPWT) distributes negative (subatmospheric) pressure across a wound surface to promote healing in clean stage III and IV wounds. An airtight system is created using special foam, sterile tubing and canister, and an adhesive film drape. The negative pressure in the wound bed increases blood flow, reduces local tissue edema, decreases bacterial colonization, and increases granulation tissue formation and mechanical wound closure [144]. It is contraindicated on wounds with exposed vital structures, necrotic material, and significant purulence or if it leads to bleeding complications.

18.4.5 Surgical Management

Proper selection of the surgical candidate is important because of the cost and postoperative recovery time, both of which can be extensive. In addition, if musculocutaneous flaps are performed, there are only a limited number that can be performed, which may be of consequence if the individual has repeated PIs.

Musculocutaneous and fasciocutaneous flaps are the procedure of choice for SCI patients who require surgical closure of the pressure injury. Because of their blood

supply, these flaps are better able to withstand pressure and shear and can be particularly useful in osteomyelitis, by bringing highly vascularized muscle tissue into the area of infection. The decision to use a particular flap or type depends on the surgeons' expertise and the size and location of the injury. It is important to approach issues that impair postoperative healing that include smoking, spasticity, nutritional concerns, and bacterial colonization (contamination from urine and feces). If there is a great deal of stool incontinence interfering with the wound, or suspected to interfere with postoperative healing of pressure injuries over the sacrum and ischial tuberosities, a temporary diverting colostomy may be considered, although most pressure injuries heal postoperatively without such procedures [157].

At the sacral area, the gluteus maximus muscle may be used entirely or in portions. At the ischium, a posterior thigh fasciocutaneous flap, inferior gluteus maximus myocutaneous flap, hamstring V-Y advancement flap, and tensor fascia lata fasciocutaneous flap can all be used to cover defects in this region. Prophylactic unilateral or bilateral ischiectomy is not recommended. At the greater trochanter, the tensor fascia lata fasciocutaneous flap is considered the flap of choice, although alternatives include the use of the vastus lateralis, inferior gluteus maximus, and rectus femoris muscles.

Postoperatively, strict bed rest is prescribed on a low-air-loss mattress or an air-fluidized bed, maintaining pressure off the surgical site as much as possible. For repairs of the sacrum or IT, the head of the bed should not be elevated greater than 15° since this position increases the risk of shear on the repaired ulcer site. There is no consensus in the literature on the necessary length of immobilization post-flap, which varies based on the size of the flap as well as the individual protocols and ranges from 2–6 weeks. Once healing occurs, passive range of motion (ROM) of the hips in preparation for sitting can be initiated. Once the hip ROM is at 90° without stress on the surgical site, sitting is initiated in short intervals, i.e., 15 min, and then with return to bed for evaluation of the surgical site. A progressive sitting program ensues, with an increase in sitting by 15 min once to twice per day. While institutional protocols vary, usually over a course of 2–3 weeks, the patient can progress to sitting up to 5 h/day completing the full protocol up to 8½ weeks [158]. Postoperative complications are common. In a recent study of post-flap complications, they found that the overall rate was 21 %, with suture dehiscence as the most common (31 %) followed by infection (25 %) [159].

Pressure injury recurrence is common and most frequently recurs at the ischial tuberosities. Smoking, diabetes mellitus, and cardiovascular disease are associated with the highest rates of recurrence.

18.5 Sexuality and Fertility in SCI

While men and women remain interested in sexual activity after SCI, their level of desire and frequency of activity decreases [160]. Regaining sexual function is extremely important and is an area of unmet need for persons with SCI [160–162]. It is reported to be the highest priority among individuals with paraplegia and the

second highest priority, after regaining arm and hand function, among individuals with tetraplegia [161]. As such, knowledge of this topic and discussion with patients at the appropriate time are extremely important.

18.5.1 Erectile Dysfunction in Men with SCI

The degree of dysfunction depends upon the level and severity of the SCI. A man with an upper motor neuron (UMN) lesion will typically have preserved reflexogenic erections, with minimal capacity for psychogenic erections. Greater than 90 % of men with complete and incomplete UMN lesions can achieve reflexogenic erections, while <10 % of men with complete UMN injuries and ~ 50 % of those with an incomplete UMN lesion may be able to achieve psychogenic erections [163]. While the majority of men with UMN lesions are able to obtain reflexogenic erections, these are often unreliable and poorly sustained and often are insufficiently rigid to achieve successful intercourse. For persons with a complete LMN lesion, ~ 12 % can achieve reflexogenic erections, with approximately 25 % being able to achieve psychogenic erections [163]. Approximately 90 % of patients with incomplete LMN injury can achieve an erection. It should be kept in mind that intrathecal baclofen, used to manage spasticity, may cause difficulties with erection and sexual function [164].

There are several treatment options available for erectile dysfunction and include oral phosphodiesterase PDE-5 inhibitors, penile implants, vacuum erection devices, vasoactive intracavernosal injections, and intraurethral alprostadil. Most commonly, men with SCI will have their erectile dysfunction treated or managed with a PDE-5 inhibitor [160].

The phosphodiesterase class of medications, most specifically the PDE-5 isoenzyme including sildenafil (Viagra) and vardenafil (Levitra) and tadalafil (Cialis), has been used with success in the SCI population with UMN lesions [165–167]. These medications appear to have similar safety and efficacy profiles, although side effect profile may vary. Since the PDE-5 inhibitors operate on the nitric oxide-induced cyclic GMP system, they are less effective in men with LMN lesions where reflexogenic erections are rare. PDE-5 inhibitors do not initiate the erection (as do intracavernosal injections) but help maintain erections via maintenance of intracavernosal levels of cyclic GMP. PDE-5 inhibitors are contraindicated in patients taking nitrates (because of hypotension) for angina or coronary artery disease, and as such patients at risk for AD should be so cautioned. Men with tetraplegia or high-level paraplegia should be cautioned about the possibility of experiencing postural hypotension for several hours after use.

The penile prosthesis, surgically implanted into the erectile tissue, was the first significant treatment for erectile dysfunction for men with SCI, with satisfactory results in 60–80 % of cases. Different types exist including malleable (semirigid) and inflatable (hydraulic). Although complication rates have improved over the years, they still may occur in ~10 % in patients with inflatable penile prostheses [168, 169]. Penile prostheses may be effective for treatment of erectile dysfunction

in men with SCI; however, it should generally be reserved for situations where all reversible erectile dysfunction treatments have failed [160].

Vacuum erection devices (pump with constriction band) can be an effective non-invasive method of managing erectile dysfunction in men with SCI [170]. Although fairly safe and effective, the device is not used frequently because of the process required for use.

Intracorporeal injections with prostaglandin E1 (Alprostadil) can induce an erection in those with UMN and LMN injuries, with a response rate of over 90 % [171]. Alprostadil injected intracavernosally works rapidly and is not dependent on the nitric oxide-PDE-5 system of maintaining high intracavernous levels of cyclic GMP (since PGE-1 stimulates higher levels of cyclic AMP, another potent vasodilator within the corpora cavernosa) [172]. Adverse effects include hypotension, bleeding, bruising, pain and fibrosis at the injection site, and priapism, especially if the dose is not carefully titrated. As with the vacuum pump, men with poor hand function may have difficulty administering the injections without help or may be dependent on a partner who is trained and willing to perform the injection. This should not be used in persons with sickle cell disease. Alprostadil has also been formulated as a small suppository (MUSE) that can be administered intraurethrally [173]. While less invasive, intraurethral preparations are not effective for treatment of erectile dysfunction in men with SCI [160].

To enhance orgasm in men with SCI, there are promising options that include microsurgery of the sensory nerves to the penis and sensory substitution training [174]. Further study is needed.

18.5.2 Fertility in Men with SCI

Most men with SCI have difficulty to father children without some assistance, with <10 % of couples achieving successful spontaneous pregnancies [175]. Erectile dysfunction, ejaculatory dysfunction, and semen abnormalities are the chief contributors to this condition. Despite this, men with SCI should maintain realistic expectations of becoming a biological father.

The majority of men with SCI are unable to ejaculate during sexual intercourse with successful ejaculations in approximately 5 % of men with complete UMN lesions and 18 % of those with LMN lesions [176]. The percentage is higher in those with incomplete injuries. Achieving ejaculation, however, does not ensure successful reproduction. Patients who experience infertility should be evaluated by a reproductive specialist soon after the decision to attempt pregnancy is made.

To obtain sperm in men who do not ejaculate, penile vibratory stimulation (PVS) and, if unsuccessful, electroejaculation (EEJ) can be attempted. PVS involves placing a vibrator on the dorsum or frenulum of the glans penis, and the mechanical stimulation produced by the vibrator recruits the ejaculatory reflex to induce ejaculation [177]. This method is more effective in men with a level of injury T10 or above (with an intact bulbocavernosus response) as compared to men with a level of injury T11 and below [178, 179]. Patients with untreated hypertension or cardiac disease

should also avoid this treatment, as PVS may increase blood pressure and can induce AD. The majority of responders will ejaculate within 2 min of stimulation onset.

Electroejaculation (EEJ) may be used for individuals who do not respond to PVS and involves electric current delivered through a probe placed into the rectum that stimulates nerves that lead to emission of semen. EEJ is contraindicated for patients with inflammatory bowel disease involving the rectum and patients on anticoagulation therapy. Similar to PVS, EEJ can provoke AD and precautions should be taken.

If these methods are unsuccessful, there are a number of surgical techniques available to obtain sperm. These include testicular sperm extraction, testicular sperm aspiration, microsurgical epididymal sperm aspiration, percutaneous epididymal sperm aspiration, and aspiration of sperm from the vas deferens [163].

Once ejaculate is obtained from the male, determination of the total sperm count and quality is undertaken. Abnormal semen quality (low sperm motility and viability as opposed to low volume) contributes to infertility in men with SCI [180, 181]. Depending upon the sperm count and viability, there are various options for intravaginal insemination (IVI) and/or intrauterine insemination (IUI). When the total mobile sperm count is low, more advanced (and expensive) methods are recommended to attempt pregnancy. The method of in vitro fertilization (IVF) involves removing sperm from the male partner and eggs from the female partner.

In cases where there are not enough motile sperm to attempt fertilization by a conventional method of IVF, a more advanced form, intracytoplasmic sperm injection (ICSI), injection of a single sperm into a single egg, can be performed, and the inseminated eggs are placed in a laboratory dish, and resulting embryos are transferred into the woman's uterus. Reasonable pregnancy rates by IVI or IUI have been obtained in couples with SCI male partners.

18.5.3 Sexual Dysfunction in Women with SCI

For women with SCI, there are a number of physical and psychological barriers to engaging in sexual activity. These include spasticity and method of bladder management with fear of incontinence, as well as low self-esteem (feeling unattractive), difficulty in meeting a partner, and a lack of confidence in sexual ability and ability to satisfy a partner [160, 182, 183]. Longer duration and lower level of injury are positive predictors of participation in sexual intercourse [184].

Genital arousal in women can be achieved via psychogenic or reflexogenic pathways and is diminished in ~25–50 % women with SCI [185]. Spared pinprick and sensory function in the T11–L2 dermatomes in women with SCI has been associated with the ability to have psychogenic genital vasocongestion (psychogenic arousal) and a greater degree of genital responsiveness than subjects with minimal or no sensory preservation in those dermatomes [186, 187]. Reflex genital arousal (manual genital stimulation) has been associated with intact reflex function in the S2–S4 dermatomes [188]. In women with complete SCI above T6, psychogenic arousal can occur in the absence of genital vasocongestion. Approximately 50 % of women report developing new areas of arousal above their level of injury, including the head, neck, and torso [189]. It is believed that

the vagus nerve may serve as a genital sensory pathway that bypasses the spinal cord and conveys vaginocervical afferent activity that can lead to orgasm [190, 191].

Most women with SCI report the ability to have penetrative sexual intercourse, post-injury. Factors interfering with intercourse include injury level, pain, spasticity, and AD during sexual activity [189]. More than 50 % of women with SCI report frequent sexual activity, and almost half of all women with SCI are able to achieve orgasm, although time to orgasm is prolonged compared to women without SCI [192–194]. Women with SCI report achieving orgasm primarily through stimulation of the genitalia and breasts [192]. The ability to achieve orgasm has been associated with presence of genital sensation and with spasticity. Women with intact bulbocavernosus and/or anal wink reflexes are usually able to experience orgasm, whereas women without S2–S5 sensation or absent bulbocavernosus and anal wink reflexes (LMN injuries) have significantly reduced ability.

Continent urinary diversion in women with tetraplegia may result in improved self-image, quality of life, and greater sexual satisfaction [160]. While one trial reported some improvement in sexual arousal with sildenafil 50 mg combined with manual stimulation and visual stimulation, overall sildenafil does not appear to result in clinically meaningful benefits in women who have sexual arousal disorder as a result of SCI [36, 160, 195].

18.5.4 Fertility in Women with SCI

SCI does not affect female fertility once menses returns. Immediately following SCI, amenorrhea occurs in 85 % of women with cervical and high thoracic injuries and 50–60 % of women overall. Within 6 months and 1 year post-injury, 50 and 90 % of women have return of menstruation. The completeness of injury does not appear to influence the menstrual cycle. Women with SCI experience menopause at similar ages to women without SCI. Once normal menstruation resumes, women with SCI can become pregnant with similar success rates as the general population. Methods of birth control should be discussed with the patient's gynecologist taking into account risks (e.g., risk of thromboembolism) versus benefits of each option.

Pregnancy presents a unique set of potential problems including the development of pressure ulcers, recurrent UTIs, increased spasticity, or decreased pulmonary function. There is a slightly increased incidence of preterm labor in SCI women [196, 197]. AD may develop in susceptible women during labor. Preeclampsia can be difficult to distinguish from AD; however, once the diagnosis of AD has been made, epidural anesthesia is the treatment of choice and should continue at least 12 h after delivery or until the AD resolves. The SCI physician should follow the patients closely in cooperation with the obstetrician.

The rate of spontaneous vaginal delivery has been reported at ~ 37 %, with an additional 31 % of deliveries by assisted vaginal delivery; the remaining 32 % delivered by cesarean delivery (198). The rate of spontaneous vaginal delivery is probably higher in patients with a level of injury below T6, whereas patients with higher-level injuries are more likely to develop AD and require assisted deliveries.

Conclusion

The medical issues discussed in this chapter have a significant influence on the acute and chronic phases of the life of persons who have sustained a traumatic spinal cord injury (SCI). Although these consequences of SCI are gaining increasing recognition, diagnostic, preventive, and treatment approaches remain diverse, and further research is needed to help inform clinical practice guidelines and overall patient care.

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Part V

Interventions

Pathophysiology of Traumatic Spinal Cord Injury

19

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Abstract

Traumatic spinal cord injury (SCI) is a drama in two acts. The first part represents the trauma itself, causing the destruction of neural tissue, i.e., the elimination of neuronal and glial cells at the primary lesion site, as well as the transection of axons transiting through the lesioned area. Additionally, damage to the vascular system will provoke hemorrhage and the disruption of the blood–spinal cord barrier. Together, these damages will induce secondary cascades responsible for cell death, enlargement of lesioned area, and further loss of neurological functions. Edema will develop in the early ischemic period triggering a phase of glutamate excitotoxicity and ionic imbalance. The ensuing mitochondrial failure is thereafter responsible for an energy depletion and oxidative stress. The rapid inflammatory response to spinal cord injury is provided by the resident microglia, but foremost by the infiltrating neutrophils and macrophages. At the end of the acute phase, the lesioned area will get enclosed and stabilized by a fibroglial scar. This chapter reviews the sequence of pathophysiological processes occurring after traumatic spinal cord injury, which constitute targets for potential protective or regenerative interventions.

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19.1 Introduction

Traumatic spinal cord injury (SCI) is an unexpected and devastating change in the life of affected individuals. Although the survival rates and the clinical management following spine injury significantly improved over the last century [1–3], no curative interventions are currently available despite intensive past and ongoing research efforts to restore lost tissues and neurological functions. To date, preservation of spared spinal cord tissue following trauma is the most important objective. Detailed knowledge on the pathophysiology and the sequence of events taking place following trauma is therefore crucial to develop adequate and optimized interventions in response to SCI. In this respect, an early surgical intervention for decompression of the spinal cord and mechanical stabilization of the spine represents the first treatment to circumvent additinal loss of spinal tissue (see chapter 7). Early decompression surgery might lead to a significant decrease in the length of acute hospital stay and the rate of complications [4].

Traumatic SCI can be seen as a drama in two acts. First, the mechanical trauma per se results in the destruction of neural parenchyma, which cannot be remediated. Mechanical injury directly disrupts axons, blood vessels (hemorrhage), and neural and glial cell membranes. The majority of primary injuries are associated with a compression due to dislocation or compression resulting in a blunt injury rather than an invasive transection (e.g., stab injury) [5, 6]. As a rule of thumb, the kinetic and the duration of the compression are the main determinants of the severity of the traumatic SCI [7, 8]. Thereafter, processes causing secondary damages are being successively activated, which lead to a propagation of the lesion within the neural tissue initially spared by the trauma. For technical reasons, the investigation of the pathophysiology of SCI has been much more extensively investigated in animal models (from rodents to nonhuman primates) than in human. Although this allowed for detailed temporal analysis and assessment of various pathological processes, the possibility of inherent differences with the human situation must be kept in mind.

This chapter reviews actual knowledge of the pathophysiology of SCI and describes the cascade of processes that might become targets for neuroprotective strategies and, eventually, regenerative therapies.

19.2 Primary Phase

In patients, traumatic SCI is provoked by physical forces acting on the spine, i.e., flexion, extension, rotation, distraction, compression, or a mixture of them. The resulting damages are referred to as the primary damages and correspond to a mechanical disruption of axons and other membranes of neural and glial cells and also in damage of blood vessels and micro-hemorrhages within the gray matter. In animal models, traumatic SCI is often simulated by direct contusion or compression of the spinal cord.

Recent epidemiological data revealed that most of the traumatic spinal cord injuries do not lead to a complete transection of the spinal cord (see chapter 1).

Hence, even if the clinical manifestation following SCI suggests a "complete" functional loss, the segments above and below the level of injury remain connected by a few axons, which correspond to an anatomically incomplete or "discomplete" lesion [9, 10]. The extent of axonal sparing required for the maintenance of significant neurologic functions below the level of injury is not precisely defined. However, residual motor functions have been observed in patients with approximately 7–8 % of all former axons reaching below the injury level [1–3, 9]. Similarly, functional studies in animal models have suggested the requirement for an axonal sparing of 1.4–12 % across the lesion site [4, 11–13]. Although few percentages of residual spared fibers are sufficient for meaningful functionality, this low relative number represents a large amount of fibers in absolute number considering, for example, that 2–2.5 million afferent fibers are entering the dorsal roots at each side of the human spinal cord [5, 6, 14].

19.3 Secondary Phase

19.3.1 Immediate

Following the primary insult, the loss of neurons and glia and the disruption of axons cause a loss of function at and below the level of the injury. Within minutes, the spinal cord swells and occupies the whole spinal canal at the injury level. Increasing spinal cord pressure beyond the arterial blood pressure leads to secondary ischemia, one of the major triggers of secondary damages [7, 8, 15]. Moreover, further neurologic functions can be transiently affected due to the spinal shock [9, 10, 16, 17].

19.3.1.1 Vascular Damages and Ischemia

Freshly injured SCI patients are particularly vulnerable for systemic hypotension as a consequence of hypovolemia, neurogenic shock, and bradycardia [18]. This hypotension, conjugated with the loss of autoregulation of intraspinal blood flow and the increased interstitial pressure, results in a hypoperfusion of the spinal tissue at the lesion epicenter [19–21]. Paradoxically, some hyperperfusion was also detected in regions adjacent to the lesion site [21]. The deleterious impact of hypotension/hypoperfusion is substantiated by the correlation associating a higher mean arterial blood pressure in the acute phase of SCI with a higher degree of long-term neurological recovery [22].

The primary injury normally spares large-caliber vessels, such as the anterior spinal artery (see chapter 2 and 5) [23–25]. Nevertheless, intramedullary distal vessels are affected by occlusion and vasospasms following SCI leading to a central ischemia despite sparing of the major supplying arteries located at the surface of the spinal cord [25]. This hypoperfusion developing from the gray toward the white matter slows and eventually blocks the propagation of action potentials along axons, contributing therewith to the spinal shock [15]. The high metabolic rate of neurons within the gray matter makes them particularly

sensitive to ischemia. In addition, damages of the small-caliber vessels compromise the blood–spinal cord barrier and lead to the extravasation of blood-borne molecules into the parenchyma, in cases of small lesions, or to the penetration of red blood cells in the cases of larger trauma with hemorrhage [26]. In this respect, the gray matter is more prone to be hemorrhagic than the white matter, because of its dense capillary network that is vulnerable to mechanical damage. Already 5 min after contusion injury, extravasation of labeled molecules is particularly pronounced in the well-vascularized gray matter [26].

Hemorrhages and swelling within the gray matter exacerbate mechanical damages and ischemia and promote spreading of necrotic cell death rostral and caudal from the initial site of injury [27]. Ischemia and necrosis trigger the inflammatory processes, such as the activation of microglia, recruitment of immune cells, and the secretion of pro-inflammatory cytokines, such as tumor necrosis factor (TNF)α and interleukin (IL)-β [28, 29]. Ischemia and necrosis also lead to an accumulation of extracellular glutamate that initiates the processes of excitotoxicity [30]. Paradoxically, following the ischemic period, the reperfusion of tissues surrounding the lesion is associated with an increased generation of detrimental free radicals.

19.3.1.2 Edema

Traumatic SCI induces the so-called cytotoxic, ionic, and vasogenic edemas. The intracellular compartment encloses approximately 70 % of the central nervous system (CNS) fluid and is richer in K^+ and much poorer in Na^+ and Ca^{2+}, as compared to the extracellular/interstitial compartment [31]. Under physiological condition, the Na^+/K^+ ATPase and the Ca^{2+} ATPase use ATP-derived energy to maintain these ionic gradients between the intra- and extracellular compartments. During ischemia, the ATP depletion will compromise the maintenance of the gradient and a massive influx of Na^+ will take place, which is accompanied by a passive influx of Cl^- through the chloride channels and water molecules via aquaporin water channels. This solute and water influx in the intracellular compartment results in cell swelling and loss of cytoskeletal integrity leading to cell death [31]. In addition, *N*-Methyl-D-aspartate (NMDA)-receptor stimulation during glutamate excitotoxicity (see below) process further favors the entry of Na^+, Cl^-, and water in neurons and glia [32]. Taken that astrocytes are 20 times more numerous than neurons in the human CNS, regulation of their cell volume will therefore also play a central role in the development of edema [31]. Importantly, as long as the blood flow is disrupted, the cytotoxic edema is not leading to an increase of tissue volume, but should be rather regarded as a fluid redistribution between two compartments.

The ionic and the vasogenic edemas result from an increased permeability of the blood–spinal cord barrier. In the first phase, the depletion of ions and water from the interstitial space triggers an increased trans-endothelial ion transport, the ionic edema [33]. Thereafter, further endothelial dysfunction, in part related to cytotoxic swelling of endothelial cells, leads to the formation of permeability pores in the blood–spinal cord barrier that allows for the passage of large plasma-derived molecules, the vasogenic edema [31].

19.3.2 Early Acute Phase

The early acute phase of SCI takes place from approximately 2–48 h post-injury and is therefore the phase seen by clinicians upon admittance of the SCI patients. During this early phase, hemorrhage is still ongoing and edema and inflammation are increasing. Cells cannot maintain their homeostasis which leads to significant necrotic cell death due to cell swelling, impairment in ATP production, the disruption of organelles, and the lysis of the plasma membrane causing the release of the intracellular content in the extracellular space and the induction of local inflammatory process [34]. In this regard, Kwon and colleagues recently reported that the concentration of specific "structural" and "inflammatory" biomarkers, e.g., glial fibrillary acidic protein (GFAP) or IL-6, in the cerebrospinal fluid (CSF) of SCI patients 24 h after injury had a good prognostic value for the severity of the functional loss, i.e., American Spinal Injury Association (ASIA) impairment scale, as well as the likelihood of conversion 6 months after injury [35].

Acute cell death by necrosis following SCI is thought to be uncontrollable [36]. As a result, fulminating secondary damage processes get induced during this period: free radical production, ionic dysregulation, glutamate-mediated excitotoxicity, and immune-associated neurotoxicity. These processes provoke additional axonal injury, cell death, and the propagation of the lesion within the surrounding spared tissue.

19.3.2.1 Excitotoxicity

In experimental models of SCI, the massive release of glutamate leads within 15 min to an excessive and persistent activation of glutamate receptors causing cell death, i.e., the excitotoxicity [30, 37, 38]. When applied on uninjured spinal cords, the glutamate concentrations reached following SCI have been shown to be toxic and sufficient to induce cell death [39]. Glutamate is a central excitatory neurotransmitter in the central nervous system which binds to ionotropic receptors, such as NMDA receptor, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainate receptors, as well as metabotropic receptors. The expression of these two receptor types is not restricted to neurons, and thus expression of several subtypes has been detected at the surface of astrocytes and oligodendrocytes [40–43]. As a consequence, glutamate excitotoxicity is not restricted to the gray matter tissue and has also been demonstrated to play a key role in white matter secondary damage [44].

Diverse sources are responsible for the immediate increase of extracellular glutamate following SCI. First, glutamate gets released by the direct mechanical rupture of cells and to a less extent from apoptotic and necrotic cells [45]. In the white matter on the other hand, the failure of the Na^+/K^+ ATPase and the collapse of Na^+ and K^+ gradients across axonal membranes following SCI will cause a reversal of the Na^+-dependent glutamate transport and consequently an important glutamate efflux [45–47]. Mechanical cell damage and transport reversal are considered to be the major mechanisms of glutamate release following SCI [45, 48]. Within the gray matter, the imbalanced ion homeostasis in neurons leads to an increase in intracellular Ca^{2+} concentrations and the local release of glutamate at the synapse. Moreover,

astrocytes can also discharge toxic amounts of glutamate in the extracellular milieu when their intracellular calcium levels are elevated. Finally, lipid peroxidation, for example, the formation of 4-hydroxynonenal products (see section below), impairs the capacity of astrocytes to reuptake glutamate and thereby contributes to its interstitial accumulation after injury [49, 50].

The mechanisms of excitotoxicity in the gray matter neurons are primarily associated with the ionotropic glutamate receptors and in particular the NMDA-receptors [51, 52]. Overactivation of NMDA-receptors results in an influx of Ca^{2+} and Na^{+} that contributes to the ionic gradient destabilization and leads to a necrotic or apoptotic cell death [39, 53]. Activation of the NMDA-receptor by glutamate promotes a delayed (between 1 and 7 days post-injury) cell death of neuron and glia [54]. Application of the receptor agonist (MK-801) to block the NMDA-receptor activation shortly after SCI improved the motor recovery and reduced the edema formation [55]. Similarly, the administration of a non-NMDA excitatory amino acid receptor agonist (NBQX) resulted in smaller lesion size and a better neurological status caudal to the injury site [30]. In addition, an excessive activation of Group I metabotropic glutamate receptors will upregulate expression of NMDA-receptors [56] and thereby also indirectly increased calcium influx. The influx of Ca^{2+} through ionotropic glutamate receptors, such as the NMDA-receptor, will lead to cell death through the activation of various secondary damage cascades including the calpain-mediated proteolytic degradation of cytoskeletal components (such as spectrin, Microtubule-associated protein 2 (MAP2), and neurofilaments), lipid peroxidation, production of reactive oxygen species (ROS), and mitochondrial respiratory failure [57–60].

Since only low amounts of AMPA-receptors can be detected on axons, the glia are considered to be the main target of glutamate toxicity in the white matter following SCI [44]. Moreover, although both astrocytes and oligodendrocytes express glutamate receptors [41, 42, 61], the latter appears to be particularly susceptible for excitotoxic cell death [61–64]. The resulting excitotoxic death of oligodendrocytes during the spreading of secondary damages provokes the loss of myelin sheath and impaired axonal conductivity.

19.3.2.2 Ionic Dysregulation

Traumatic SCI, and in particular the excessive glutamate signaling, rapidly alters the ionic membrane flux, leading to a relevant increase in the intracellular Na^{+} and Ca^{2+} concentrations and decrease in intracellular K^{+} levels [44, 46, 65–68]. The high intracellular Ca^{2+} concentration will further inhibit the mitochondrial respiration and result in an energy depletion [57]. This depletion of energy due to anoxia and decrease in ATP production causes a suppression of the Na^{+}/K^{+} ATPase and the Na^{+}/Ca^{2+} exchanger activities and therefore hinders the mechanism of ionic homeostasis [44, 46, 69–71].

The failure of the Na^{+}/K^{+} ATPase results in a depolarization of the axonal membrane causing an even higher Na^{+} influx through voltage-gated Na^{+} channels [68]. In 1992, Stys et al. provided evidence that these conditions provoke the reversal of the Na^{+} – Ca^{2+} exchanger activity and thereby to a greater influx of Ca^{2+} [72]. The high

density of voltage-gated Na^+ channels at the nodes of Ranvier makes axons more vulnerable to excessive Na^+ influx, as compared to the somatic compartment of neurons. This abnormal Na^+ influx, accompanied by a passive influx of Cl^- and water, is responsible for swelling of cells and edema [73]. The improper intracellular sodium–potassium balance exacerbates the cytotoxic edema [74]. High intracellular Na^+ concentration activates Na^+/H^+ exchanger rising intra-axonal pH by proton influx, leading to axonal acidosis which further increases calcium membrane permeability [75–78]. Administration of Na^+ channel blockers in animal models of SCI provided a better functional outcome and smaller lesion size, supporting the view that Na^+ entry is a key player in early secondary injury mechanisms [75, 79].

Ca^{2+} acts as secondary messengers in diverse cellular processes. During the induction of cell death, high intracellular levels of Ca^{2+} activate protein kinases and phospholipases, increase the ROS generation, and cause mitochondrial dysfunction [38, 80]. Additionally, high intracellular concentrations of Ca^{2+} activate the calpains, which are Ca^{2+}-dependent non-lysosomal cysteine proteases degrading cytoskeletal proteins, such as neurofilament subunits and microtubule-associated protein 2 (MAP2), which are important for axonal integrity and function [58, 81–83].

19.3.2.3 Mitochondrial Failure

Mitochondria are crucial to the cellular energy metabolism and generate ATP via the oxidative phosphorylation. Mitochondria possess a double membrane which defines four compartments: the outer mitochondrial membrane (OMM), the intermembrane space (IMS), the inner mitochondrial membrane, and the matrix. The outer mitochondrial membrane (OMM) forms a loose barrier for the intermembrane space and allows for molecules up to 5 kDa in size to pass through, for example, via the voltage-dependent anion channels (VDAC) [84]. In contrast, the inner mitochondrial membrane (IMM) is only passively permeable to oxygen, water, and carbon dioxide under physiological conditions. These differences in permeability are essential to establish and maintain a proton gradient across the inner mitochondrial membrane, which is central for the generation of ATP [85, 86].

The mitochondrial proton gradient is generated by the so-called electron transport chain (ETC). The first and largest component of the ETC, Complex I (also named NADH dehydrogenase), catalyzes the oxidation of NADH in the IMS and uses the energy liberated to pump protons in the IMS [86]. In contrast to other tissues, mitochondria in the CNS, and especially those present in neurons, contain large amounts of Complex I, which is prone to generate reactive oxygen species under physiological and pathological conditions [87]. Under physiological conditions, however, the coenzyme Q and the cytochrome c are responsible to carry the electrons along the various complexes of the ETC. This electron transport will contribute to the proton gradient in the intermembrane space and will end with the reduction of molecular oxygen within the matrix [85, 86, 88, 89].

The Complex V of the ETC, also called the ATP synthase, is responsible for the generation of ATP, the main energy carrier of the body. Complex V is embedded in the inner mitochondrial membrane and acts as a proton channel. Under physiological conditions, protons are forced through the channel, and ATP will be synthesized

from this electrochemical gradient, provided that ADP and free phosphate are available. If the proton gradient is insufficient, Complex V will use ATP to pump protons back into the intermembrane space, thus consuming energy instead of generating ATP [85, 86, 88, 90].

In addition to the synthesis of ATP, mitochondria are important reservoirs responsible for buffering and maintaining the cytosolic Ca^{2+} levels. After SCI, however, the cytosolic Ca^{2+} concentrations significantly increase within the first 15–60 min and persist abnormally high for days. In the first phase, the Ca^{2+} influx will be largely buffered by a mitochondrial uptake, leading to an increase in ATP production [91]. The side effect of a higher activity of Complex I is however the increased production of ROS [88, 91]. Nevertheless, the mechanism by which calcium concentration influenced the generation of reactive oxygen species within the mitochondrial compartment is still debated [57, 92].

Further toxic accumulation of excessive Ca^{2+} within the mitochondria will trigger an unspecific permeabilization of the inner mitochondrial membrane through the opening of the mitochondrial permeability transition pores (mPTP) [90, 93]. The molecular structure of the mPTP remains unclear [94]. The opening of the mPTP enables molecules of up to 1.5 kDa to pass the inner membrane into the mitochondrial matrix. It will also lead to a severe breakdown of the proton gradient and therefore inactivates the ATP synthesis. Moreover, the attempt of Complex V to restore the proton gradient by actively pumping protons into the intermembrane space will lead to a massive ATP consumption [90, 95, 96]. Opening of the mPTP will also enable an influx of water and other molecules into the mitochondrial matrix and provoke swelling and disruption of mitochondrial membranes, resulting in a release of several proapoptotic factors within the cytosol. These factors will induce programmed cell death, i.e., apoptosis, necroptosis, and autophagy, as long as the ATP levels suffice, otherwise necrosis will occur [85, 97–100].

19.3.2.4 Free Radical Production and Lipid Peroxidation

Oxygen is particularly prone to participate in the generation of reactive free radicals, particularly in association to the mitochondrial ETC, which is the main generator of ROS and free radicals in cells. As mentioned above, mitochondria intensify the production of ROS following SCI, although the role of Ca^{2+} accumulation in this increase is unclear [57]. Moreover, the last step of the ETC consists in the reduction of molecular oxygen, which gives rise to a superoxide under physiological conditions. Although superoxide radicals are not very reactive per se, they can react with nitric oxide to produce peroxynitrite, a highly reactive nitrogen species (RNS). Moreover, a second reduction reaction on the superoxide will generate to peroxide, and a third reduction reaction will result in the formation of the highly reactive hydroxyl radicals [101].

In addition to the mitochondrial free radical generation, the acidosis observed after SCI promotes the release of the tightly sequestered intracellular iron stocks from the ferritin and the transferrin. The spontaneous oxidation of Fe^{2+} into Fe^{3+} will also generate superoxide radicals. Moreover, the reaction of Fe^{3+} with hydrogen

peroxide will generate highly reactive hydroxyl radicals through the so-called Fenton reaction [102].

The toxic ROS and RNS generated under pathological conditions react on numerous targets [102]. Lipid peroxidation is likely the most deleterious ROS-associated damage occurring after SCI. Lipid peroxidation proceeds according to three distinct steps starting with the initiation in which highly reactive oxygen species react with the polyunsaturated fatty acids of the membrane and take an electron from the allylic carbons to generate a reactive lipid. This reactive lipid will interact with a superoxide radical to form a lipid peroxyl radical. The latter will react on the neighboring fatty acid and cause again the production of a reactive lipid. The propagation of this reaction will continue until the reactive lipid quenches with another radical or until no more unsaturated lipids are available. This final step, the termination, generates two toxic peroxidation products, namely, 4-hydroxynonenal (HNE) and 2-propenal [49, 102–104]. The carbonylation of amino acids is also an important free radical-associated damage responsible for the increased protein oxidation observed after traumatic SCI [105]. Similarly, RNS can nitrate the tyrosine residues to give rise to 3-nitrotyrosines (3-NT), which is a specific marker for protein damage [103].

The processes of protein oxidation and lipid peroxidation play an important role in the secondary damage cascade following SCI. For instance, lipid peroxidation will exacerbate ionic imbalance by destabilizing various membranes, e.g., cytoplasmic membrane or the endoplasmic reticulum [103]. Furthermore, lipid peroxidation contributes to the inhibition of the Na^+/K^+ ATPase, which worsens the intracellular accumulation of Na+ [106, 107]. The oxidative stress can also attack enzymes of the mitochondrial respiratory chain, alter DNA, etc. and results in a metabolic collapse with ensuing necrotic or apoptotic cell death [108].

19.3.2.5 Inflammation

As for other organs, lesions of the spinal cord induce strong inflammatory and immunological responses. Intriguingly, SCI evokes substantially more potent and widespread neuroinflammation than brain injury [109] and elicits a multi-organ systemic reaction. Thus, following spinal cord lesion, systemic inflammation provokes damages to the lungs, kidneys [110], and liver [111, 112]. The inflammatory processes within the injured spinal cord are complex, and their net impact, either neurotoxic or neuroprotective, often depends on their duration and timing. The inflammatory responses after SCI involve various cellular components, such as microglia, neutrophils, and macrophages, and also molecular components, such as cytokines, prostanoids, and the complement system.

Under physiological conditions, complement factors are synthesized at low levels within the CNS by astrocytes, microglia, neurons, and oligodendrocytes [113]. The complement factors are not only important effectors for the host immune response to various types of pathogens, they are also activated by tissue damage [113]. Following SCI, the complement is activated almost immediately and then increases locally within 1 day and persists thereafter chronically [113, 114]. This elevation of the complement is also detectable in the serum of SCI animal models

and may become a useful biomarker in human patients [115]. The local production of complement factors by CNS-resident cells and from infiltrated inflammatory cells, as well as a transient leakiness of the blood–spinal cord barrier, results in the accumulation of these factors within the injured spinal cord [113]. Although the contribution of serum-derived complement proteins vs. local production is still unknown, the local secretion contributes to the establishment of a gradient facilitating the recruitment of phagocytic cells to the lesioned tissue for clearance of myelin debris among others. Recent studies have demonstrated that inhibition of complement system was beneficial during the acute phase of SCI (<7 days). However, its absence at later time point was associated with a larger lesion size and reduced functional recovery, as a consequence of impaired glial scar formation and increased peripheral immune cell infiltration [115].

Similarly, the cellular component of inflammation gets mobilized early after SCI. In particular, microglia react within minutes to cellular damages and to the release of ATP and nitric oxide in the extracellular milieu [29, 116, 117]. In a SCI mouse model, the induction of IL-1β expression revealed the activation of local resident microglia as soon as 5 min post-injury [29]. In human, the activation of microglia could also be detected in the earliest time point investigated, i.e., 30 min post-SCI, and the elevated secretion of IL-1β by microglia has been confirmed 5 h post-SCI [118]. Early secretion of IL-1α and IL-1β by the activated microglia during cell death-induced sterile inflammation promotes the infiltration of leukocytes toward the lesion site [29, 119]. With their progressive accumulation, infiltrating neutrophils and macrophages become the primary source of IL-1β secretion in the lesion site within 1 day [119].

The early recruitment of peripheral cells in the lesion is central to the pathophysiology of SCI, for instance, the infiltration of neutrophils, which is already extensive within the first 24 h and peaks within 3 days post-injury [120, 121]. However, neutrophils are ephemeral at the site of injury. Hence, following a maximal accumulation of neutrophils at day 3 in a rat SCI model, only half of the neutrophil population was still present 1 day later, and very few neutrophils were detectable 2 weeks post-injury [120]. Importantly, Allen et al. 2012 [122] reported that neutrophils acquire neurotoxic properties following an IL-1-mediated blood–brain transmigration. Moreover, neutrophils secrete proteases, elastase, and myeloperoxidase and release ROS and cytokines, such as TNFα, which altogether exacerbate the damages associated with the initial trauma and contribute to the recruitment of additional inflammatory cells [123, 124]. Similarly, the population of infiltrating T-lymphocytes followed a comparable kinetic as seen for the neutrophils. However, a residual population corresponding to approximately 10 % of T-lymphocytes present at 3 days was still detectable in the lesion site up to 10 weeks post-injury [120].

The size of the phagocytic cell population invading the lesion site is proportional to the extent of damages [125]. In agreement with their early activation, microglia have been reported to be the main phagocytic cells for the clearance of cellular debris during the first day following SCI [126]. Following the neutrophil wave, hematogenous macrophages immigrate in the lesion site from approximately day 3

onward and accumulate in number until day 7–10 [120, 126–128]. During this massive wave of phagocytic cell invasion, incoming macrophages become the predominant phagocytic cell type and they will sustain their phagocytic activity, whereas the microglia progressively retire from clearance activity with no or little phagocytosis detected 3 days after injury [126, 129]. In contrast to neutrophils, the macrophage population, following its accumulation peaks, only slowly resolves from the spinal cord. Hence, in the lesion, 50 % of the macrophage population present at accumulation peak was still visible 55 days after injury in a rat SCI model and 45 % at the latest time point investigated in this study (10 weeks) [120]. The lack of lymphatic drainage within the spinal cord could partly explain the longer persistence of leukocytes, although the alymphatic nature of the spinal cord following injury has been recently questioned [130].

As compared to responses following peripheral nerve injuries, a more pronounced and more sustained polarization of microglia and macrophages toward the pro-inflammatory M1 phenotype have been observed following SCI [131–133]. Moreover, the number of classically activated macrophages (M1) progressively increased over time going from 10 % $CD86^+$ macrophages 1 week post-injury to 30 % $CD86^+$ at 10 weeks post-injury. Recruited M1 macrophages secrete pro-inflammatory mediators and are thought to be the major source of toxic inflammatory factors following SCI [133]. Furthermore, M1 macrophages express 16-fold higher level of chondroitin sulfate proteoglycans (CSPGs) than M2-polarized cells, which could further negatively impact the regeneration potential within the spinal cord [134]. The study performed by Prüss and colleagues demonstrated that the M2-polarized macrophage population decreased from 60 to 20 % from the first to the tenth week post-injury [120]. The paucity of anti-inflammatory M2 macrophages observed after SCI might be responsible for the prolonged pro-inflammatory status, which is deleterious for the neural tissue [133]. Among others, M2-polarized macrophages secreted IL-10, a cytokine with robust anti-inflammatory activity [135]. The neuroprotective activity of IL-10 administration following SCI appears to be associated with its ability to increase the expression of anti-apoptotic genes [136, 137]. The observation that 20–40 % of the M2-polarized macrophages transplanted into an injured spinal cord switched to a M1 phenotype, whereas this does not occur in the intact spinal cord, underscores the strong M1-inducing environment prevailing following SCI [133].

Accumulated evidence shows that infiltrating neutrophils and macrophages are simultaneously involved in processes of damage and repair of the neural tissue following SCI [122, 123, 133, 138–140]. For example, blood-borne monocytes/macrophages and resident microglia recruited to the injury site contribute to the debris clearance by phagocytosis [28, 126]. The bulk of immune cells recruited on the other side secretes pro-inflammatory cytokines, e.g., TNFα, interleukins, and interferon promoting the progression of secondary injuries [141]. Moreover, although invading macrophages have been classically associated with the further destruction the neural tissue surrounding the lesion site, the phagocytic clearance capacity provided by the macrophage is even higher following peripheral nerve injury. Hence,

the lower phagocytic activity seen following SCI might be paradoxically responsible for a poor regenerative response [142–145]. This apparent deleterious/beneficial duality results from the capacity of immune cells to be polarized into different phenotypical subsets with pro- and/or anti-inflammatory activities at different time points and distances from the lesion [119, 129, 138, 146].

19.3.2.6 Axonal Dieback and Wallerian Degeneration

The induction of acute axonal degeneration (AAD) is responsible for the bulk of axonal degeneration occurring during the early phase, i.e., the first 48 h post-SCI [147]. Acute axonal degeneration shares common downstream effectors of axonal degeneration, e.g., activation of the cysteine protease calpain, with the Wallerian degeneration [148, 149]. However, the process of acute axonal degeneration is characterized by the early influx of Ca^{2+} into the axons, as soon as 15 min after injury, through pores transiently opened by the mechanical stress [148, 149]. It has been recently shown ex vivo that clearance of extracellular Ca^{2+} directly after injury protects axons from acute axonal degeneration. Using in vivo calcium imaging, Williams and colleagues demonstrated the axons accumulating high levels of Ca^{2+} after SCI where at risk to undergo acute axonal degeneration [148]. Immunodetection of neurofilaments and electron microscopy revealed that the number of axons remaining in the dorsal column at the level of the lesion was reduced by more than half already after 1 day after compression injury in a rat model [150].

At the end of the acute axonal degeneration phase, remaining transected axons will undergo a distinct degenerative process at their proximal and distal segments. For a few hours, the axonal stumps retain their morphology and enter the so-called “latent” phase of Wallerian degeneration [149]. The end of transected axons will be capped by retraction bulbs, which are similar in morphology to growth cones. In contrast to the latter, however, the retraction bulbs have a disorganized microtubule network, which is associated with an impaired axonal regeneration capacity [151]. Stabilization of the microtubule network by the application of paclitaxel following axonal transection reduces the formation of retraction bulbs and the axonal retraction of the proximal stumps, whereas disorganizing the microtubule network of growth cones using nocodazole turns them into retraction bulbs [151].

The distal stump, which is separated from the cell soma, will disintegrate via Wallerian degeneration within the first 24–48 h post-injury in rodents or over several days in humans [152, 153]. In addition to transected axons, the signaling cascade leading to Wallerian degeneration can also be triggered following failure in axonal transport [154]. After the latent phase of Wallerian degeneration, fulgurant fragmentation along the full length of the axon takes place stochastically between the remaining axons. In the case of axonal transection, the fragmentation appears to spread anterogradely within individual axons [152, 155]. Although mechanisms underlying acute axonal and Wallerian degenerations remain largely unknown, the influx of calcium is clearly playing a pivotal role in these processes [59]. However, whereas the withdrawal of extracellular Ca^{2+} was shown to be protective against the

acute axonal degeneration in an ex vivo model, it is rather ineffective against the Wallerian degeneration, which depends primarily on intra-axonal Ca^{2+} pools [59].

Wallerian degeneration shares similarities with apoptotic processes, such as being triggered by a signaling cascade and the exposition of annexin V on the plasma membrane [155]. However, the modulation of classical pro- or anti-apoptotic factors, e.g., Bax, Bak, Bcl2, etc., does not prevent or influence the course of Wallerian degeneration, thereby suggesting two distinct signaling cascades for apoptosis and Wallerian degeneration [156, 157].

19.3.2.7 Demyelination

Oligodendrocytes are particularly vulnerable following SCI and tend to undergo necrotic and apoptotic cell death. In a rat model, the number of axons demyelinated due to the acute loss of oligodendrocytes by apoptosis peaks approximately 24 h post-injury [158]. Oligodendrocytes are sensitive to excitotoxicity since they express receptors for glutamate, i.e., AMPA, kainate, and NMDA-receptors [40]. Shortly after SCI, the glutamate concentrations rise at levels toxic for oligodendrocytes provoking a Ca^{2+} influx and the activation of signaling cascades leading to cell death [159, 160]. In addition, oligodendrocytes are particularly prone to oxidative stress damages due to their high metabolic activity, low amounts of glutathione, high content of iron, and their abundant peroxisomes [161]. Moreover, oligodendrocytes are submitted to the free radicals released by the infiltrating neutrophils and activated microglia. Finally, immune cells invading the lesion site release pro-inflammatory cytokines, such as TNFα, IL-2, and interferon (IFN)γ, and proteases promoting apoptosis in oligodendrocytes [36, 162–164].

The apoptotic processes steadily decrease the number of oligodendrocyte over at least 3 weeks in a rodent model of SCI [165, 166]. This loss of oligodendrocytes causes a demyelination that compromises axonal function and preservation. Days, even weeks, after the initial trauma, a wave of oligodendrocytic apoptosis propagates within as much as four segments from the injury site [167, 168]. This remote apoptosis observed within the white matter is thought to result from the Wallerian degeneration which deprives the oligodendrocytes from trophic factors formerly supplied by the axons [165, 166, 169]. Since one oligodendrocyte myelinates several axons, the removal of one oligodendrocyte by apoptosis may result in demyelination of adjacent axons, otherwise considered as spared and therefore aggravates the loss of neurological functions distal to the lesion.

Polarization of microglia and macrophages into the pro-inflammatory M1 state, due to increased iron uptake and immediate increase in TNFα production, promotes apoptosis and necroptosis of neurons and oligodendrocytes [132]. Studies based on IL-1α knockout models and IL-1 receptor antagonist revealed that this cytokine plays a central key role in the induction of inflammation and apoptosis in oligodendrocytes following SCI [170]. Moreover, M1 microglia and macrophages, as well as neutrophils and astrocytes, express the pro-inflammatory cytokine TNFα [29]. At the site of injury, the mRNA expression of TNFα increases dramatically after trauma with a first wave peaking already 1 h post-injury and decreasing by 24 h [29, 171]. Modulation in mice models has shown that this early

flood of TNFα is toxic for neurons and oligodendrocytes and induces their cell death [172–174].

Following injury, oligodendrocytes induce the expression of Fas-receptors, which are involved in caspase 3 and caspase 8-mediated programmed cell death [175]. Interaction of the Fas-receptor with the Fas-ligand found on the surface of activated microglia and invading lymphocytes induces apoptotic cell death [175–177]. Demjen and colleagues demonstrated that the application of Fas-ligand-neutralizing antibodies improved motor outcome and reduced apoptosis in neurons and oligodendrocytes after partial dorsal transection of the spinal cord in a mouse model [178]. Shortly after, Casha et al. reported an improved motor recovery and better survival of oligodendrocytes and axons in a Fas-deficient mouse model [176]. However, better survival of neurons was not observed in this model. Therefore, a Fas-receptor–ligand interaction might play an important role in oligodendrocytic cell death and demyelination following SCI.

19.3.3 Subacute Phase

The subacute phase (2 days to 2 weeks post-injury) is characterized by the continuation of an intensive phagocytosis of cellular debris accumulated in the lesion site [28]. In addition, during the subacute phase, the astrocytes located at the periphery of the lesion proliferate and become hypertrophic, which can be easily visualized by the detection of intermediate filament GFAP. These astrocytes initiate the formation of a glial scar physically sealing the injury site. The prominent astrocytic scarring detected in rodents has been reported to be significantly more restricted in humans [179].

19.3.3.1 Fibroglial Scar

Astrocytes are a major component of the fibroglial scar developing around the lesion site [180]. Astrocytes react quickly to SCI by changes in their gene expression, hypertrophy, and process extension [181]. The fibroglial scar consists of various cells and extracellular matrix (ECM) developing in and around the lesion. Hypertrophic astrocytes dominate in the peri-lesion, but the lesion core contains a heterogeneous mix of cells including NG2+ glia/oligodendrocyte precursor cells, meningeal and/or vascular fibroblast, pericytes, ependymal cells, and phagocytic macrophages [182].

The scar tissue forming after SCI is often referred to as the “glial scar” because of the presence of numerous astrocytes. However, the non-glial component in scars, comprising a significant amount of pericytes, and connective tissue originating from ECM deposited by fibroblasts should not be neglected [183]. Under physiological condition, there are approximately ten times more astrocytes than pericytes within

the spinal cord parenchyma. However, 2 weeks following SCI in a mouse model, the lesioned segment contained twice as much pericyte-derived cells than astrocytes [184]. In this mouse model, cells originating from pericytes occupied the central regions of the scar tissue and were surrounded by astrocytes. Also, in the first days following injury, many pericytes found in the lesion site had lost contact with the blood vessels and migrated in the surrounding tissue where they secreted large amount of ECM molecules [184]. Pericytes which detached from blood vessels started to express markers characteristic for fibroblasts, such as fibronectin, and constituted the main source of scar connective tissue [184].

Disruption of the meninges (see chapter 2) by traumatic SCI is associated with infiltration of meningeal fibroblasts, which form a fibrotic scar and contribute to the inhibitory environment [185], and expression of repulsive guidance molecules [186] and can result in spinal cord tethering [187, 188]. The glial scar also stabilized the injured parenchyma by reestablishing its physical and chemical integrity, closing the blood–brain barrier, reducing the infiltration of non-CNS cells, and limiting possible infection [189]. Historically, the astrocytic scar has been regarded as the main impediment for axonal regeneration. However, recent data have demonstrated that the scar has also a pro-regenerative function [190]. Hence, depletion of the astrocytic component of the fibroglial scar has been shown to exacerbate the lesion, increase axonal retraction, and decrease the expression of pro-regenerative genes in a mouse model of SCI [191]. Moreover, the absence of scar forming astrocytes had no impact on the accumulation of CSPGs at the lesion site.

Necroptosis, a form of cell death distinct from apoptosis and necrosis, has long been a neglected process in SCI pathology. This newly recognized type of "programmed necrotic cell death" can be initiated even in the presence of classical caspase inhibitors used to block apoptosis. Evidence that necroptosis plays an important role as a mechanism of neuronal cell death after SCI was recently provided by Liu and colleagues [192]. Necrostatin-1, a specific necroptosis inhibitor, was found to be neuroprotective after SCI and decreased lesion size after SCI through a protective action on mitochondria [192–194].

19.4 Chronic Phase

The transition from the subacute to the chronic phase is characterized on the one hand by the maturation of the astrocytic scar and on the other hand by the regenerative axonal sprouting [195]. The various temporal patterns of the regenerative response of specific tracts may reflect the different regenerative mechanisms of specific neuronal populations [195]. The chronic phase begins approximately 6 months after injury and extends for the rest of the patients' life. The process of Wallerian degeneration remains active for many years in order to remove the severed axons and the respective cell bodies [98, 196, 197]. It is considered that 1–2 years post-injury, the lesion and the associated functional deficits have for the most part stabilized.

19.4.1 Cyst Formation

The progressive enlargement of the lesion area and the formation of a cyst walled by reactive astrocytes is a hallmark of traumatic SCI [187, 198]. The process of cavitation is the result of ongoing apoptotic neuronal and oligodendroglial cell death. Moreover, recent work demonstrated that M1-polarized microglia and macrophages present in the lesion site induce reactive astrocytes to undergo necroptosis through TLR4/MyD88 signaling [199, 200]. Since astrocytes are known to support the survival of neurons and oligodendrocytes, their loss could further promote cell death of the latter.

After establishment of the post-traumatic cyst, about one third of SCI patients develop syringomyelia (see chapter 9) [201]. A complete SCI and an age above 30 years at injury represent the major risk factors for developing syringomyelia. On average, patients are diagnosed with syringomyelia 15 years after their injury [201]. Syrinx formation causes pain and further neurological deficits. Treatment of syringomyelia is still a major challenge. For example, even after a surgical intervention to address their syringomyelia, 39 % of patients with incomplete SCI report a worsening of their condition 5 years after surgery [202]. Unfortunately, little is known regarding the pathophysiological processes involved in the syrinx formation, hindering thereby the development of preventive intervention.

Alterations of CSF dynamics are believed to be an important cause of syrinx expansion. Hence, obstructions in the subarachnoid space near the lesion could increase CSF flow and thereby cause an influx into the syrinx [202–204]. Decompression by laminectomy and expansion duraplasty are expected to contribute to a more favorable outcome [187, 205]. Indeed, patients who underwent a laminectomy or a dura opening show a significantly lower incidence of syrinx formation, unless important canal stenosis was present [206].

Hypotheses on syrinx formation and expansion have been mostly developed from computational modeling on human MRI data or mechanical models imitating the syrinx formation. Recently, however, a rat model for SCI-associated syrinx formation, based on the application of kaolin to induce an arachnoiditis after a contusion or excitotoxic lesion, has been reported [207, 208]. The induction of arachnoiditis appears to play a crucial role for the development of syringomyelia [207]. These studies demonstrated that the functional and structural disruption of the blood-spinal-cord-barrier is a potential source of fluid for the formation of the syrinx [208, 209].

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The Current Status of Neuroprotection for Spinal Cord Injury

20

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Abstract

Spinal cord injury (SCI) resulting in impaired neurological functions creates suffering and economic burden. Directly after the injury, the conservation of tissue at the lesion site and the preservation of the connectivity through the injury epicenter have highest priority. This tissue preservation will not only reduce neurological deficits, but also and allows for more rapid and extensive recovery. Advances in clinical care intended to accomplish this goal include early surgical decompression, support of blood pressure, and the subject of this chapter – experimental neuroprotective therapeutics. The scientific foundation of neuroprotection is that "harmful" secondary injury processes extend and distribute the tissue loss caused by the primary injury event. Existing clinical knowledge together with preclinical experimental evidence has supported phase III clinical trial translation of some neuroprotective agents in the past four decades. Although some have had positive results, the magnitude of improvement was small, and associated complications and controversy surrounding certain therapeutics diminished their role in SCI care. However, these trials generated knowledge valuable to guide current work. Neuroscientists continue to develop new therapeutic approaches by demonstrating neuroprotective efficacy in small and large animal models. A consensus now exists that the preclinical data set to support the expensive process of translation must be very robust and include a well conducted independent replication. Primary endpoints for pivotal clinical trials have been clarified on the basis of aggregate experience and extensive studies on the

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natural history of SCI. "Secondary injury" consists of numerous mechanisms, and the probability of a robust protective effect of a single agent is small. It is necessary to design rational combinations of therapies to increase efficacy.

20.1 Introduction

> Scientists often have a naive faith that if only they could discover enough facts about a problem, these facts would somehow arrange themselves in a compelling and true solution.
> Theodosius Dobzhansky

The capability of central nervous system (CNS) tissue for self-repair after severe injury is often insufficient to restore important neurological functions. Due to its small size and axonal concentration, the spinal cord is especially vulnerable to traumatic damage. The *primary injury* to the spinal cord results from an abrupt physical distortion such as occurs with a diving accident or a military blast injury. Cascades of molecular, cellular, tissue, and organ level events, many of which are pathophysiological, are initiated and propagate the tissue loss caused by the instantaneous primary injury. These events, collectively known as "secondary injury," are thought to develop in proportion to the primary insult with a consequent progressive loss of residual gray and white matter around the injury epicenter. Secondary injury starts *immediately*, and its duration depends on which mechanism of pathophysiology is considered (e.g., excitotoxicity, ionic dysregulation, free radical toxicity and lipid peroxidation, mitochondrial and membrane failure, axonal disintegration, apoptosis and cell death, demyelination, inflammation) (see chapter 19), but can last at least weeks. The secondary injury concept is a generalization whose value may be superseded as more specific knowledge of post-injury processes is developed. *Neuroprotection* is also a broad concept applied to many types of neural injury referring to the *attenuation* of *impending injury*. The possibility to provide neuroprotection has been proven in certain settings, e.g., tissue cooling increases the brain and spinal cord's tolerance to ischemia when initiated prophylactically [34, 267]. In these scenarios, tissue cooling *neuroprotects* the CNS *during* ischemia that would otherwise cause neuronal death.

However, more commonly neuroprotection refers to reduction of damage that would otherwise occur *after* an unpredictable event such as traumatic SCI. The development and testing of neuroprotective agents has largely followed emerging knowledge of pathomechanisms of secondary injury. Thus, early efforts focused on problems such as lowered spinal cord blood flow (SCBF) for which experimental evaluation techniques existed [272]. Current efforts are directed to control molecular events for which newer biomarker measurements are available.

The CNS has unique tissue properties, responses, and vulnerability; neuronal cells extend processes for long distances with *high complexity* and *specificity*. Neurons have high metabolic requirements and must maintain membrane function within narrow parameters. CNS glia also have complex functions including regulation of neurotransmitter levels and formation of myelin. The blood-brain barrier

prevents the crossing of many classes of drugs, cells, proteins, and other molecules from the blood into the CNS extracellular space. Thus, specialized pharmacokinetic and pharmacodynamic studies are necessary to understand delivery and distribution to the brain and spinal cord. These include the administration route, bioavailability, serum, CSF and tissue levels, half-life, route of elimination, and metabolism to active and inactive products, including the impact of focal blood-brain barrier disruption. Critical issues such as a therapeutic window, dose-response, and adverse or secondary effects must be determined in preclinical animal models and phase I/II human studies. Neuroprotectants range from physical processes that affect the entire body (hypothermia) to drugs, ions, and specially engineered proteins and other biomolecules.

There has been a high failure rate of neuroprotective therapies applied clinically in stroke, traumatic brain injury, and SCI despite many impressive experimental studies in animals. To understand the reasons for this, and to increase efficiency and effectiveness, emphasis has been directed toward both the need for greater rigor in preclinical testing and clinical trial design [123, 196], increased reporting of negative results [229, 304], and the development of quantitative biomarkers.

Another issue to consider is that the distinction between primary and secondary injury is *artificial* because much of what is called secondary injury is directly triggered by the primary insult, as is a bruise following a blow to an extremity. Thus, the extent to which the consequences of primary injury can be attenuated may be limited. Another key distinction is between secondary injury and secondary insult, the latter being, e.g., an additive insult influenced by therapeutic management such as prolonged hypotension or by concomitant injuries such as hypoxia from pulmonary injuries. This chapter will summarize current knowledge of neuroprotective strategies in SCI discussing the major lessons so far learned and prospects for the near future.

20.2 Non-pharmacological Strategies for Neuroprotection

20.2.1 Surgical Decompression

The relief of ongoing pressure on the spinal cord and stabilization of the spine are indicated after SCI when either significant compression or instability is present. *Decompression is the most direct neuroprotective procedure.* Without spinal cord decompression, many other neuroprotective strategies are *futile*. If spinal cord compression raises the tissue pressure, ischemia may compromise tissue that might otherwise survive [46, 78]. Early decompression after SCI was assessed in several rodent models. These have shown improved behavioral and anatomical outcomes when decompression was performed earlier, e.g., 6 and even 12 h post-SCI, rather than 24 [284]. There may also be a role for adding dural enlargement to spinal cord decompression. Four-hour post-injury durotomy with allogeneic duraplasty reduced spinal cord cavitation, inflammation, and scar formation when compared to injury or durotomy only control animals [293]. A recent clinical study showed that

following SCI, duraplasty improved estimated spinal cord perfusion more than spinal laminectomy decompression alone [248]. Recently, even the acute decompression of necrotic spinal cord tissue has been assessed as a neuroprotectant in large animal models, thus the definition of effective spinal decompression after SCI is in evolution.

Although evidence in animal models shows a benefit to early spinal cord decompression, the optimal clinical timing has been a leading controversy in neurosurgery in recent decades and remains without conclusive evidence. Concerns regarding early surgery have included the safety of acute surgical manipulation of the spinal cord; safety of transportation to specialized care centers; availability of skilled spine surgeons, anesthesiologists, and operative teams at all hours; availability of imaging; and vulnerability of acutely damaged spinal tissue to fluctuations in blood pressure during anesthesia. Substantial published evidence has addressed these concerns supporting the safety of early surgery [101, 112, 134, 331]. The spine surgery culture has shifted to recognize the value of early surgery. An evaluation of the clinical effectiveness of decompressive surgery after SCI took place with the STASCIS Study (Surgical Timing in Acute Spinal Cord Injury). This multicenter, international, prospective, nonrandomized study analyzed the effects of early (<24 h post-SCI) versus late decompression (≥24 h post-SCI) [101]. From 313 patients enrolled, 222 were assessed at the 6-month post-SCI interval; 19.8 % of the early surgery cohort showed a ≥2 grade improvement in AIS grade versus 8.8 % in the late group. There were some imbalances in the relative severity of injury between the groups, but it is evident that early surgery was not harmful in this trial. Thus, surgical decompression should be considered the first significant neuroprotective goal of SCI therapy in concert with other guidelines and potential experimental treatments.

20.2.2 Support of Blood Pressure

Ischemia is a prominent pathomechanism of SCI secondary injury. Spinal cord blood flow (SCBF) is normally autoregulated so that flow matches metabolic demand over a range of blood pressures (BP). However, after SCI, autoregulation is disrupted, and SCBF becomes more linearly linked to systemic BP [324]. SCI patients frequently have low BP due to neurogenic shock. Inadequate BP is a risk factor for poor neurologic patient outcome [150, 205, 330], presumably by exacerbating ischemic damage. Therefore, support of adequate BP is a key to effective neuroprotection. Recently, it has been shown that intraspinal tissue pressure may be used to guide the mean arterial pressure to optimize spinal cord blood flow [341]. This type of monitoring is well established in brain injury and it is logical to extrapolate to SCI [333].

20.2.3 Infection

Recent studies have provided evidence that SCI patients with infections such as pneumonia have less neurological recovery [95]. Thus, infection is a

"disease-modifying factor." Schwab and colleagues developed rodent models where an acute immune deficiency state associated with SCI increased vulnerability to infection due to alterations in monocyte function. This has been described as the spinal cord injury-induced immune depression syndrome (SCI-IDS) [42, 265, 266]. Additionally the risk of bacterial infection seemed to be injury-level dependent in an SCI mouse model [42]. A current prospective, multicenter, international clinical protocol, the SCIentinel study, is examining the hypothesis that the severity of immune depression is dependent on injury severity and injury level [180]. Based on this evidence, avoidance of infection is critical in SCI and could be neuroprotective. Recently, it has been learned that the population of bacteria in the gut is altered by SCI [136]. Emerging studies are assessing the impact of the altered microbiome on neurological recovery and complications.

20.2.4 CSF Drainage

CSF drainage is known to influence SCBF and has achieved prominence as a preemptive strategy to reduce paralysis due to spinal cord *ischemia* during aortic surgery. The ability of CSF drainage to improve SCBF after SCI is less certain. Spinal cord perfusion pressure (SCPP) is calculated to be proportional to the average pressure head (mean arterial blood pressure – MAP) minus the venous resistance that has been estimated as cerebrospinal fluid pressure (CSFP). Thus, by reducing CSFP, SCBF may be increased. In clinical studies of thoracoabdominal aneurysm repair combined with CSF drainage, an 80 % reduction in the relative risk of postoperative neurological deficits has been reported [63, 65, 316]. After SCI, efforts to maintain SCBF include correction of spinal shock due to lack of sympathetic tone and increased capacitance by keeping MAP >90 mmHg using vasopressors. Pharmacologically increased MAP is thought to compensate for the failure of SCBF *autoregulation* due to loss of tonic activity of sympathetic neurons. Lowering CSFP may be another alternative to increasing SCBF. A prospective randomized study including 22 patients evaluated the safety and feasibility of CSF drainage and the correlation with neurological recovery at 6 months post-SCI [186]. A CSF drain was placed prior to surgical decompression and maintained for 72 h in all subjects. Subjects were randomized to have CSF drained or not drained, with a drainage threshold of 10 mmHg (the typical value of CSF pressure). After rostral decompressive surgery, there was a marked increase in distal CSFP as well as the onset of a pulsatile waveform. These changes indicated that the CSF measurements prior to surgical decompression (recorded from the lumbar cistern) did not represent the entire CSF space due to rostral occlusion by unreduced bone and disc fragments. Thus, calculations of SCPP prior to decompression were inaccurate, and a reduction in apparent SCBF occurred after decompression when more accurate CSFP values were recorded. In this study, the CSF drainage was conservative; the CSFP remained well above the target value due to restrictions on the rate of drainage per hour and drain closure when intensive patient assessment by nursing was unavailable. Although the study was not powered to assess efficacy nor the patients stratified according to injury level, the authors conclude that there was no neurological

detriment or benefit due to the intervention. In a recent study, a pressure recording catheter was inserted into the intrathecal space and then "wedged" between the damaged spinal cord and the dura. The pressure reading was much higher than that of the CSF and considered to represent elevated *spinal cord tissue pressure* [341]. This finding indicates the weakness of relying on oversimplified formulae for SCPP that assumes spinal cord tissue pressures are reflected by CSFP. A recent porcine SCI study has shown that neither elevating MAP with pressors nor releasing CSF *alone* improved SCBF other than transiently, but the *combination* of both manipulations increases SCBF in a more sustained manner [228].

20.2.5 Therapeutic Hypothermia

The impact of tissue cooling on *ischemia* in the brain and spinal cord has been studied for more than six decades. Interest in hypothermia partially derived from nature because temperature and metabolic rates are linked. Hibernating mammals dramatically reduce their core body temperature minimizing their metabolic needs. A key idea is that by reducing metabolic requirements, tissue survival during states of low blood flow is improved. Studies in anesthetized dogs by Bigelow and colleagues showed a nearly linear relationship between core temperature and reduced oxygen consumption down to the lowest survivable temperatures (28°C) [29]. Pontius, DeBakey, and colleagues reported that in dogs cooled systemically to 29.4°C, the incidence of post-thoracic aorta occlusion-related paralysis was reduced from 65% to zero [253]. In the 1960s, hypothermia was employed for neuroprotection to allow temporary circulatory arrest for complicated aneurysm surgery [81]. An important *advance* was the finding that that mild hypothermia (e.g., 33°C), which is much safer clinically, also had significant neuroprotective effects in rodent stroke models [44]. As of 2016, hypothermia has been studied extensively in several clinical settings. The most compelling current *clinical* data to support a neuroprotective benefit for hypothermia are from clinical trials in post-cardiac arrest comatose patients [27]. Hypothermia has been tested extensively in traumatic brain injury (TBI) and to a lesser extent in SCI. Despite experimental evidence of reduced tissue loss and improved brain function in animal models [75], multiple clinical trials have failed to show a benefit of post-traumatic hypothermia in adult or pediatric brain trauma [271], other than for transient control of raised intracranial pressure. SCI studies commenced in the 1960s. Maurice Albin and Robert White created one of the first neurocritical care units, located at the Cleveland Metropolitan General Hospital. Numerous experiments examining the impact of hypothermia on the brain and spinal cord were performed. In a study published in 1968 [5], primates were subjected to weight-drop contusion SCI, and after a delay of 4 h, one group underwent local perfusion cooling with a target spinal cord temperature of 10°C maintained for 3 h. The results were impressive, all treated animals recovered, and none of the controls showed substantial recovery. Now, with decades of additional experience, the 1968 results with localized

hypothermia seem too good to be true, in part due to increased skepticism about extremely distinct results. In other animal models, hypothermia has been shown to mitigate several aspects of secondary injury cascades. There is modulation of inflammation [76], with reduced neutrophil infiltration [52], less glutamate release [166] and excitotoxicity, and reduced cellular energy metabolism [352]. The preponderance of experimental evidence indicates systemic cooling methods to be more effective [212] than epidural cooling [48].

Several small clinical studies of spinal cooling have been performed, but none has had a sufficiently robust design to provide conclusive evidence of efficacy due to small patient cohort numbers and a lack of suitable controls. The use of hypothermia is greatly underreported based on discussions with senior neurosurgeons who participated in unpublished studies. Since it is not a drug, it is relatively easy to apply hypothermia. Clinical experiments in the 1970s emphasized locally applied cooling due to the influence of Albin and White's publications. Bricolo and colleagues treated eight neurologically complete acute SCI patients with 2 h of subdural cooling using 5°C saline irrigation. Motor and sensory recovery was reported in four subjects with 2 recovering ambulation [41]. Hansebout and colleagues studied the effect of local epidural cooling in a dog model of spinal cord compression to assess optimal treatment duration [182, 340]. Based on favorable results with 4 h of cooling, they then recruited ten patients with complete SCI to undergo early surgical decompression and local extradural cooling within 8 h of complete SCI. The dural temperature at the injury site was maintained at 6°C for 4 h using a suspended extradural saddle (cord temperature was not recorded). A factor complicating interpretation was the delivery of dexamethasone, 6 mg every 6 h for 11 days, and then tapered until the 18th day. This study had a mean follow-up of 1.9 years. Of six subjects with thoracic SCI, four were unchanged, one became ambulatory, and another had sensory recovery. Of four subjects with a cervical injury, three were unchanged, and one showed motor and sensory recovery [148]. These studies occurred before the publication of the important ASIA impairment scale (AIS) in 1982. Hansebout and Hansebout published a long-term follow-up of the original cohort with ten additional patients enrolled in local cooling and dexamethasone treatment. Results were reported by adapting their previous scoring system to the AIS scale. From the total of twenty treated patients categorized as baseline AIS-A, there was improvement in thoracic injuries of 16.7 % to AIS-B, 33.3 % to AIS-C, 16.7 % to AIS-D, and a mean sensory descent of 2.5 levels per patient. For the cervical cohort, there was improvement of 35.7 % to AIS-B, 21.4 % to AIS-C, and 7.2 % to AIS-D, with a mean motor descent of 0.92 levels per patient [147]. These recovery rates are much better than the published natural history for cervical and thoracic injuries [302, 355], but we know that the reproducibility of small cohorts is poor and robust trial design is needed to obtain valid conclusions regarding therapeutic efficacy [194]. Critique of this study included the contradictory evidence available for the use of steroids, the possibility of improved outcomes as the natural evolution following early decompression surgery, and

the interpolation of the clinical data [321]. Given the current information, it would be better not to combine steroids and hypothermia in a clinical trial.

Currently, systemic hypothermia after acute SCI in subjects with motor complete paralysis is under evaluation in an observational prospective cohort study sponsored by the University of Miami/The Miami Project to Cure Paralysis (ClinicalTrials.gov identifier: NCT01739010) at Jackson Memorial Hospital, Miami, FL. Systemic cooling is achieved using an intravascular cooling catheter advanced centrally through the femoral vein. The target temperature is 33°C at a maximum cooling rate of 0.5°C/h, MAP is maintained >90 mmHg, and rewarming begins after 48 h at a rate of 0.1°C/h. A preliminary report of 14 patients scored as AIS-A on admission indicated conversions of three patients to AIS-B, two to AIS-C, and one to AIS-D, with similar rate of complications to the historical control group [204]. In a more recent publication [74], data from 35 subjects with initial AIS-A cervical injury was presented. The rate of conversion to higher AIS grades exceeds than expected from historical controls. Both studies indicate a delay to initiate cooling with an average of 5.8 h for subjects rapidly transferred to the institution, followed by 2.7 h to achieve the target temperature. All patients underwent surgical decompression at an average of 16.5 h after injury. There was no relationship between the timing of cooling onset and neurological outcome. The majority of complications were pulmonary, and the incidence was similar to that in recent series if adjusted for injury severity. Although the data is promising, it remains difficult to isolate the efficacy of hypothermia without a randomized control group. A new study, acute rapid cooling of the traumatically injured cord (ARCTIC), is designed to randomize patients to control and cooling temperature groups.

20.2.6 Dietary Adjuvants/Restrictions

There has been interest in the influence of dietary factors on CNS inflammation and oxidative stress and diet's contribution to neurodegenerative diseases such as Alzheimer's [145, 221] and epilepsy [173]. The positive influence of a *ketogenic diet* on the incidence of seizures in children has been known for a hundred years [153] and the favorable impact of fasting for millennia. Ketogenic diets reduce circulating glucose and increase ketones as an energy substrate in the CNS. The ability of a ketogenic diet to improve cerebral metabolism after TBI was reviewed by Prins and Matsumoto [260]. In rodents, ketones can reduce free radical generation from mitochondria during stress induced by excess levels of glutamate [218]. Reduction in reactive oxygen species (ROS) has also been observed with caloric restriction. Following unilateral cervical crush hemisection, *every-other-day fasting* (EODF) leads to reduced injury size, increased gray matter sparing, improved ipsilateral forelimb function, increased functional *Tropomyosin receptor kinase B* (trkB) receptor levels, and increased plasticity of corticospinal tract (CST) axons [252]. EODF animals weighed 8% less than controls at the end of the experiment. Blood glucose and *β-hydroxybutyrate* ketone levels varied inversely throughout the study.

In a rat model of cervical hemi-contusion, Tetzlaff and colleagues mimicked the effects of fasting using a 3:1 ratio regimen of ketogenic diet starting 4 h after injury, with a return to standard diet 12 weeks post-injury. Animals receiving this diet showed improved behavioral recovery, reduced lesion size, increased gray matter sparing, with an increase in the vascular transporters GLUT1 and MCT1 [310]. The post-injury weight gain was similar between the ketogenic and control group. These investigators also studied daily food restriction to 75 %, equivalent to the total food intake of EODF animals, after T10 moderate contusion injury. This continuous caloric restriction did not yield evidence of protection, whereas EODF improved locomotor recovery [168]. When EODF was studied in a mouse model, no behavioral or histological improvement was observed after a T10 crush SCI, and β-hydroxybutyrate levels failed to rise substantially in the first week post-injury despite prominent loss of body weight [311]. These data indicate that the responses in mouse and rat models differ; thus, caution should be exercised in the extrapolation of rodent data to humans.

Creatine is a popular health supplement whose delivery has been shown to maintain ATP homeostasis in TBI models. Rabchevsky and colleagues tested the neuroprotective effect of 2 % creatine supplementation of rat chow given for 4–5 weeks prior to T10 New York University (NYU) or Infinite Horizon device-delivered (IH) contusion injuries on tissue sparing and locomotor recovery (see chapter 25). They also tested the effect of continuation or cessation of the diet *after* the T10 IH injury. Although no overall effects on locomotor recovery or white matter sparing were found, the creatine supplemented groups in the IH experiment had smaller lesion volumes and more gray matter sparing [261]. IH injuries were found to be more focal in distribution than NYU injuries. These differences provide another example of the variations arising in "standard" injury models and the caution that is needed in extrapolating results for human trial design where injuries are heterogeneous [85].

The neuroprotective effects of *long-chain omega-3 polyunsaturated fatty acids* (PUFAs) such as docosahexaenoic acid (DHA) are being studied. The effects of acute IV delivery of DHA at 30 min, 1 h, and 3 h post-injury were investigated in a T10 spinal cord compression model. Thirty-minute but not 3 h delivery was associated with substantial neuroprotection with improved neuron and oligodendrocyte survival, reduced inflammation, and significantly improved locomotor scores. Reductions in the oxidation of lipids, proteins, RNA and DNA, and COX-2 expression were found [159], as well as evidence of reduced axonal cytoskeletal damage, demyelination, and preservation of serotonergic innervation below the injury level [338]. A recent study performed in a T6/7 mouse clip compression model found reduced edema, tumor necrosis factor (TNF)-α, nitrotyrosine formation, and glial fibrillary acidic protein (GFAP), FAS ligand, BCL2-associated X protein (BAX), and B-cell lymphoma 2 (BCL2) expression when DHA was administered 30 min after injury [245]. Translation of this therapy has been limited due to lack of cGMP (current good manufacturing practice) grade DHA indicating the difficulty of obtaining clinical grade formulations that affects many agents suitable for clinical testing. The therapeutic window for DHA is brief, apparently true of most neuroprotectants, and its strong safety profile supports acute administration.

20.3 Pharmacological Strategies Tested in Human Clinical Trials

20.3.1 Methylprednisolone Sodium Succinate (MPSS)

Studies with MPSS have been important in the evolution of SCI clinical trials raising critical questions about the benefit/risk equation for therapeutic neuroprotection, the relative weight to be assigned to robust prospective research designs as compared to other forms of cohort studies [102] and the importance of a substantial body of evidence in justifying an emerging treatment as a treatment standard. The student of neuroprotection is referred both to the many reviews of this topic and also to the primary studies and subsequent critiques [160], many of high quality. As an anti-inflammatory drug, there are numerous indications for methylprednisolone and a long history of clinical use in the CNS [234]. Likewise, complications related to its use have been reported for almost 40 years [312]. After experimental SCI, MPSS administration was shown to inhibit lipid peroxidation [142, 143], facilitate extracellular calcium recovery [348], and reduce inflammatory responses [158], white matter neurofilament degradation [40], and macrophage/microglia infiltration [239]. Given the large data set indicating beneficial effects in preclinical studies and the absence of an effective clinical treatment for acute SCI, there was enthusiasm for clinical translation of MPSS. There were three prospective randomized studies of MPSS in SCI lead by Bracken and colleagues. The First National Acute Spinal Cord Injury Study (NASCIS I) was initiated in 1979 and completed in 1984. No significant difference in improvement was found between subjects that received doses of 1000 mg or 100 mg of MPSS for 11 days [35, 38]. However, the high dose was associated with an increased relative risk for case fatality and wound infection. The NASCIS II study increased the dose and reported neurological improvement for MPSS versus placebo if the treatment was started *within 8 h of injury* (30 mg/kg loading dose, 5.4 mg/kg/h for infusion continued for 23 h) [36, 37]. A third NASCIS trial was published in 1997, in which a 24-h treatment period was compared to a 48-h treatment course. There was no placebo control, and MPSS was compared to trilizad, a non-glucocorticoid lipid peroxidation inhibitor. The trial included the Functional Independence Measure as well as ASIA motor and sensory scores as principle outcomes. A Japanese multicenter trial reported following NASCIS II, using the same pharmaceutical protocol, also found a benefit in the MPSS group [238]

A decade after publication of the NASCIS II data, the use of MPSS was widespread and in some cases not supported by the clinical trial evidence. A counter opinion framed MPSS as an inappropriate “gold standard” treatment in acute SCI care. Viewed retrospectively, this early assignment of “gold standard” status is considered to have been unwise and damaging to the study of other therapeutics [160]. However, at the time the excitement that something worked in SCI overshadowed a more measured evaluation of the study results. NASCIS III indicated an advantage to prolonged (48 versus 24 h) treatment if drug delivery was started 3–8 h post-injury, but no advantage if initiated within 3 h [39]. When the NASCIS II protocol

was tested in France, no significant differences in outcomes between methylprednisolone and nimodipine were found [247]. A small prospective trial in Japan assessed complication rates with the NASCIS II MPSS protocol versus placebo in patients with cervical injury (and associated cervical stenosis) that did not undergo surgical decompression. A higher rate of pneumonia and GI bleeding was observed in the MPSS group. It should be noted that the average patient age was 61 years old [230]. Further, seven retrospective studies took place in the 1990s, six in the USA and one in Ireland; these have included more than 1300 patients and have shown equivalent motor outcomes in between the steroid and non-steroid groups with slight trends or significance toward the increase of complications in the MPSS groups [119, 121, 122, 152, 206, 257, 259].

MPSS is the most extensively tested pharmacological neuroprotective agent in the SCI field, but evidence to support its use in acute SCI for either the 24- or the 48-h regimen remains controversial due to issues in the research designs and the incidence of associated complications. Three multicenter, randomized clinical trials were completed to address the efficacy of MPSS, and only the NASCIS II has clearly indicated a benefit for neurological scores. The potential increase in serious medical complications including infections, sepsis, respiratory complications, pulmonary embolism, gastrointestinal hemorrhage, pancreatitis, delayed wound healing, worsening of head injury outcomes, and death is a concern. Furthermore, access to the study data has been limited, and concerns have been raised about the control group results and the lack of submission of the data to the FDA to obtain an approved indication [60]. Altogether, these critiques seem harsh treatment of large well-intentioned RCTs, but given the high incidence of serious complications in SCI [133], it is unwise to use an agent that may add to this morbidity. In summary, due to the limited evidence of efficacy in clinical trials and the risk of medical complications, the use of MPSS is only recommended by the American Association of Neurological Surgeons/Congress of Neurological Surgeons (AANS/CNS) *as an option* which may be supported by clinicians balancing the evidence of side effects toward the limited clinical evidence and the circumstance that there might be no other available therapeutic to offer at the moment [336].

20.3.2 GM-1 (Monosialotetrahexosylganglioside)

GM-1 belongs to a family of glycosphingolipids that contain only one sialic acid residue; gangliosides are abundant in the nervous system [73, 146]. GM-1 is believed to have trophic effects. These include inducing neurotrophin-3 (NT3) release with further activation of the TrKC receptor [262], mimicking nerve growth factor (NGF) activity, and activation of the TrKB receptor [104]. Synthetic derivatives of GM-1 – LIGA4, LIGA20, and PKS3 – have been shown to protect neurons from glutamate-induced death [223]. Clinically, GM-1 was tested in stroke before SCI [9]. Despite several trials in stroke, its efficacy remained unclear [SASS trial] [113], possibly due to methodological issues [7], not unlike those that affect SCI clinical trials.

The first clinical report testing GM-1 in SCI was a small prospective, randomized, placebo-controlled, double-blinded trial [117, 118]. Thirty-seven patients received a loading dose of MPSS 250 mg followed by 125 mg every 6 h for 72 h, together with GM-1 100 mg/day within 72 h post-SCI, continued daily for 18–32 days. Thirty-four patients were available at 1-year follow-up, and the authors reported a significant improvement in AIS motor scores ($p=0.047$) and Frankel grade ($p=0.034$) with no adverse effects attributed to GM-1. The following year, the Sygen multicenter, prospective, double-blind, randomized, and stratified study was initiated. The Sygen study is one of the most important trials the SCI field has performed and the *largest* SCI therapeutics trial ever conducted. 797 patients were enrolled from 1992 to 1997. All patients were first treated according to the MPSS NASCIS II protocol and then randomized to placebo, low-dose GM-1 (300 mg loading dose and then 100 mg/day), or high-dose GM-1(600 mg loading dose and then 200 mg/day) for 56 days [116]. Follow-up with AIS and Benzel classification continued until 52 weeks post-injury. The primary endpoint of the study was "marked improvement" at 26 weeks, defined as a two-grade change in the Modified Benzel Classification from the baseline AIS grade. Although there appeared to be a more rapid neurological recovery in the Sygen-treated group, there was no difference in the overall treatment groups at 26 weeks. However, several interesting trends were observed in the data including more improvement in the AIS-B treatment group and efficacy trends in sensory, motor, bowel, and bladder function as well as ceiling effects in subjects that were initially AIS-C and AIS-D. A ceiling effect means that, e.g., a subject enrolled as AIS-D cannot show a 2 grade improvement and should not have been recruited to the trial. Adverse events did not differ between the treatment groups. There was no true placebo in the GM-1 study because MPSS was considered the gold standard at that time. In summary, the pivotal clinical trial for GM-1 failed to meet its prospectively set primary outcomes. The primary efficacy measure of the Sygen study was a high bar, and statistically significant differences were only observed on post hoc analysis. There is no subsequent clinical study available to validate or disprove the previously mentioned clinical evidence nor has much further experimental evaluation been published [47]. Given the logistical investment to conduct a phase 3 RCT in SCI, it is rare that a therapeutic is further tested after the failure of a well-designed study, even if redesign or stratification might lead to a different result. Currently a GM-1 loading dose of 300 mg followed by 100 mg/day for 56 days after the administration of methylprednisolone within the first 8 h of injury (as per NASCIS II protocol) is recommended by the AANS/CNS as an option (if available) for the treatment of acute SCI. Data from the GM-1 study has proven useful as a comparator for other clinical studies and to help define the natural history of SCI recovery [97, 302]. One of the most striking aspects of the GM-1 story is the paucity of published preclinical data in SCI models prior to the initiation of clinical trials. In the only study reporting the combination of MPSS (30 mg/kg) and GM-1 in a rat model of contusions of graded severity, the *acute* combination of both drugs blocked the neuroprotective effects of MPSS. In that study, no effect of acute administration of GM-1 was noted, and MPSS alone was neuroprotective in mild and moderate contusion but had minimal benefit after severe contusion [61].

20.3.3 Magnesium

Magnesium salts and polyethylene glycol are used extensively in medicine. Magnesium neuroprotective properties have been evaluated in animal models for 25 years [167]. Magnesium can block N-Methyl-D-aspartate (NMDA)-type glutamate receptors and reduce calcium influx to cells attenuating glutamate excitotoxicity [361]. Other reported effects include decreased apoptosis [200], improved electrophysiological conduction, reduced lipid peroxidation [315], and normalized lactate levels after SCI [240].

After brain and spinal cord injury, local levels of magnesium are depleted contributing to mitochondrial dysfunction. In rodents intraperitoneal high doses of $MgSO_4$ (600 mg/kg) given *immediately after* SCI have resulted in early functional recovery and preservation of spinal cord ultrastructure when compared to small doses (100 mg/kg) [174]. Although the effects of magnesium are noteworthy, the doses postulated to induce neuroprotection may be too high and could produce respiratory depression or cardiac arrest in the acute clinical injury setting. Additional preclinical studies assessed magnesium formulations with more efficient blood-brain barrier penetration. One strategy is to combine magnesium salts with polyethylene glycol (PEG) to increase penetration. PEG can have several effects on drug delivery, including increasing the serum half-life of nanoparticles, enhancing brain barrier permeation, and directly supporting membrane repair acute SCI [32]. Several patents have described pharmacological properties of Mg-PEG compounds that achieve higher CSF concentrations as compared to Mg alone, optimal IV delivery rates, and calculations of Cmax, $AUC_{0\text{-}\infty}$, and $T_{1/2}$ for different PEG-magnesium formulations (US Patents 8840933, 8852566). A series of animal studies has examined the relative effects of PEG, Mg^{2+}, and their combination compared to saline after SCI on tissue preservation and neurological outcomes. Kwon and colleagues conducted a detailed study to assess the neuroprotective effects of either $MgCl_2$ or $MgSO_4$ combined with PEG at two different doses, 127 μmol/kg or 254 μmol/kg across four time points for initial delivery: 15 min, 2, 4, and 8 h after injury. Two, four, or six infusions spaced 6 or 8 h apart were compared. Using lesion size as a marker of neuroprotection, it was found that early delivery was more protective, the anion (Cl versus SO_4) made no difference, the higher concentration was superior, more IV doses were superior to fewer, and a 6-h dose infusion interval was best [186, 188]. Other groups have reported improved tissue sparing with $MgSO_4$ (300 mg/kg) + PEG versus saline controls in a severe T3 clip compression injury, with no significant differences when compared with either treatment alone [80].

Recognizing that IV CNS magnesium therapy could be limited by low CSF and tissue levels, and the previously reported results by Kwon and colleagues, Medtronic Inc. developed a polymer formulation that enhances magnesium accumulation at the injury site. Acorda Therapeutics licensed this formulation as AC105 (Mg/PEG) and designed a phase II double-blinded, randomized, placebo-controlled study of the safety, tolerability, and potential therapeutic activity of a regimen of six sequential AC105 doses in patients with acute SCI. The first dose was to be given in progressively earlier cohorts, 12, 9, and 6 h after injury with all doses delivered over 30 h (ClinicalTrials.gov

Identifier: NCT01750684). Although the study was terminated in 2015, no results have been yet disclosed. Multiple other studies of magnesium in various indications have reported mixed results. A recent large-scale trial (1700 subjects) assessing the prehospital use of magnesium sulfate in stroke did not find a therapeutic effect [274].

20.3.4 Riluzole

Riluzole is an extensively studied off-patent benzothiazole drug. The neuroprotective effects of riluzole were first reported in ischemia [222]. It counteracts glutamate-mediated neurotoxicity by inhibiting the release of glutamate from presynaptic terminals [56, 227], increasing high affinity glutamate uptake [11], and inhibiting sodium channels, by maintaining voltage-regulated sodium channels in the inactivated state [23, 258]. Riluzole crosses the blood-brain barrier [22]. The molecule was developed in France as an antiepileptic, and there have been several clinical trials for psychiatric conditions such as generalized anxiety disorder, major depressive disorder, and obsessive-compulsive disorder [128]. The only FDA-approved indication of riluzole is to prolong the time interval before assisted ventilation is needed in amyotrophic lateral sclerosis (ALS) patients [233]. Given the established safety record and known safe dose levels, the regulatory pathway to test such drugs in SCI can be much simpler than for novel therapeutics.

Experimental studies have assessed the effect of riluzole delivery in a variety of SCI models. Excessive glutamate is *neurotoxic* by leading to accumulation of intracellular Ca^{2+} that activates calpain proteases that break down cytoskeletal components such as spectrin, Microtubule-associated protein 2 (MAP-2), and neurofilament. Pretreatment of rats with 8 mg/kg of riluzole 15 min before and 2 h post 25 g/cm NYU impact to the T10 spinal cord substantially reduced activated calpain and MAP-2 loss in neurons [297]. Four or 8 mg/kg before and at the *onset* of reperfusion in aortic cross-clamping prevented ischemia-induced necrosis and cytoskeletal proteolysis [195]. Rats receiving riluzole (2 mg/kg 30 min post-thoracic compression and then BID for 10 days) recovered somatosensory evoked potentials (SSEPs) and had smaller lesion volumes [313]; 5 mg/kg 15 min after compressive SCI improved gray matter and selective white matter sparing with better hind-limb coordination and strength [278]; 8 mg/kg post S2 transection reduced spasticity [177], but 10 mg/kg caused motor weakness. Only two studies assessed a *clinically meaningful therapeutic window*, 8 + 30 mg/kg of MPSS, 2 and 4 h post-contusion promoted tissue sparing and recovery in Basso, Beattie, and Bresnahan (BBB) scores [235]. Eight mg/kg BID 1 and 3-h post-C7 cervical clip compression and continued at 6mg/kg BID for 7 days showed improved SSEPs, tissue preservation, reduced apoptosis, and improved locomotor scores [344]. In this study, a striking difference in the benefit between the 1- and 3-h post-injury groups is observed indicating the *brief therapeutic window* to reduce secondary injury.

In 2010 the North American Clinical Trials Network (NACTN) initiated a prospective multicenter phase I trial to evaluate the pharmacokinetics, safety, and effects of riluzole in acute SCI (ClinicalTrials.gov Identifier: NCT00876889).

Thirty-six patients were enrolled; the dose was 50 mg PO within 12 h of injury, continuing BID for 14 additional days. The trial did not have a concurrent control group, but the comparison group was formed by 36 matched patients meeting the eligibility criteria that received standard of care treatment in NACTN centers from October 2005 to November 2012 enrolled to the NACTN data registry. The authors report a significantly higher mean motor score in cervical patients treated with riluzole ($p = 0.021$, 31.2 points versus 15.7 points in the control group) from admission to 90 days, with no serious adverse events or deaths related to riluzole [132]. A phase 3 study is now underway for riluzole. A well-designed multicenter, double-blind, randomized, placebo-controlled trial will test a dose of 100 mg BID during the first 24 h post-SCI, followed by 50 mg BID (day 2–14 post-SCI) in an international study enrolling subjects with acute cervical SCI [99] (Clinical trials.gov identifier: NCT01597518). The study is aimed to be completed in 2018.

20.3.5 Minocycline

This broad-spectrum bacteriostatic antibiotic is the most lipid-soluble tetracycline available and has excellent penetration into the CNS. Minocycline has gained interest for its neuroprotective and anti-inflammatory properties in several neurodegenerative diseases including Huntington's [54], Parkinson's [163, 164], schizophrenia [53], and multiple sclerosis [360]. In animal models of SCI, minocycline has been shown to reduce caspase-3 activation, attenuate cell death, reduce lesion size [202], decrease activated microglia/macrophage density, oligodendrocyte death and CST dieback [306], inhibit cytochrome-C release and astrogliosis [326], and inhibit lipid peroxidation [295]. Minocycline moved rapidly through preclinical testing to clinical evaluation due to its prior extensive safety record as an antibiotic and established toxicity limits.

From 2004 to 2008, the University of Calgary conducted a single-center, double-blind, randomized, placebo-controlled, phase II study, to test the safety and estimate outcome changes after an IV minocycline infusion started within 12 h of SCI. Surgical decompression occurred during the first 24 h post-SCI, and minocycline was delivered IV BID until 7 days post-SCI (ClinicalTrials.gov identifier: NCT00559494). MPPS was not given to the subjects. Each had a lumbar catheter placed to allow CSF sampling. To achieve serum levels similar to those found to be effective in experimental models, the authors treated the first five subjects with an IV loading dose of 200 mg, followed by 200 mg BID for 7 days, and then assessed serum and CSF minocycline trough and peak levels. Based on this information, the dose was then revised to an 800 mg loading dose, reduced by 100 mg in each subsequent dose until 400 mg, and then maintained BID for the remainder of the 7 days. The authors found no statistically significant difference in the primary outcome (ISNCSCI motor scores up to 1 year) [49]. Only one subject showed a minocycline linked adverse event with a transient elevation of liver enzymes. Although the study was not powered sufficiently to prove therapeutic efficacy, patients with complete cervical SCI showed a 14-point motor increase and patients with incomplete cervical SCI a 22-point improvement over placebo. Post hoc analysis indicated that the

higher minocycline doses were associated with a greater degree of motor recovery. These data shows the importance of obtaining pharmacokinetic data *from CSF* to assess the adequacy of dosing strategies. A related serum biomarker study showed that subjects receiving minocycline had lower levels of the light chain of neurofilament than those receiving placebo [184]. Minocycline is now being assessed in a multicenter, randomized, double-blind, placebo-controlled Canadian phase 3 trial enrolling subjects with acute cervical SCI. Minocycline will be infused centrally BID at 800 and 700 mg on day 1, 600 and 500 mg on day 2, and 400 mg thereafter from day 3 through 7 (Clinical trials.gov identifier: NCT01828203). An estimated enrollment of 248 subjects is aimed to be completed in 2018.

20.3.6 Cethrin

RhoA is a major G-protein regulator of the cytoskeleton. Rho's activity state is regulated by whether it's in the GTP (active) or GDP (inactive) state. Active RhoA promotes *growth cone collapse* by activating Rho kinase and also activates apoptosis in the injured spinal cord [83]. C3 transferase, a bacterial enzyme, ADP ribosylates asparagine 41 in the effector-binding domain of Rho, irreversibly preventing its activation [72], one result of which is to prevent axonal growth cone collapse when confronted by inhibitory molecules in the spinal cord. Cethrin is a synthetic molecule that consists of C3 transferase with an added cell membrane transport sequence [214, 343]. Key experiments included in vitro studies where primary retinal neurons treated with C3 transferase extended neurites on myelin substrates. After optic nerve crush and C3 transferase treatment, axons crossed the lesion and grew distally [203]. Experiments in a mouse hemisection model of SCI with C3 transferase showed significant differences in the modified BBB analysis and long-distance regeneration of CST fibers [72]. The cell membrane transport sequence enhanced dural penetration in rodent studies. This sequence alteration is claimed to make extradural delivery through the dura feasible [214].

The Rho inactivator BA-210 was trademarked as Cethrin by BioAxone BioSciences Inc., and a phase I/IIa multicenter, nonrandomized, open-label, dose-escalation trial for patients with complete cervical or thoracic SCI (ClinicalTrials.gov Identifier: NCT00500812) was conducted [100]. From the 48 patients enrolled, 32 completed the 12-month follow-up. Treatment was delivered during surgical decompression with Cethrin mixed within a fibrin sealant placed on top of the dura mater. Five doses were tested, 0.3, 1.0, 3.0, 6.0, and 9.0 mg. Most of the subjects were treated between 24 and 72 h after injury [231]. The most compelling data from the study is a dose-dependent effect on recovery of cervical motor scores with the maximum observed recovery with the 3 mg dose (27 points improved from baseline). Anderson and McKerracher analyzed the data from pooled dose groups using the method of last observation carried forward and compared to the Sygen control group, the European Multicenter Study about Spinal Cord Injury (EMSCI) database, the US Models Systems and Waters published recovery data. The analysis showed a conversion rate from AIS-A to AIS-C of

33 % in cervical patients and 7 % in thoracic patients, the cervical conversion rate being higher than reported in the Sygen control group. The cervical total motor score improvement of 18.6 ± 17.3 exceeds the other data sets, although the EMSCI recovery rates are close. More than 40 % of cervical subjects in the pooled Cethrin group recovered 2 or more neurological levels, which is also higher than usual. BioAxone announced a multicenter, randomized, double-blind, placebo-controlled phase IIb/III trial for Cethrin to begin for patients with acute cervical SCI (ClinicalTrials.gov Identifier: NCT02053883), aimed for completion in 2016. Subsequently, BioAxone licensed Cethrin to Vertex Pharmaceuticals Incorporated in late 2014 and withdrew the study. Cethrin appears now under the name of VX-210, and a new phase IIb/III study (randomized, double-blind, placebo-controlled) sponsored by Vertex launched in early 2016 for patients with acute cervical SCI. The trial is expected to be completed in 2018 (ClinicalTrials.gov Identifier: NCT02669849).

20.3.7 Naloxone

In the late 1970s, the opiate antagonist naloxone was found to reverse the septic shock-like consequences of IV delivery of endotoxin. B-Endorphin, an opiate agonist, was released in response to shock [155]. In 1981, Faden, Jacobs, and Holaday published an experiment in cats where, following a severe C7 cervical contusion, naloxone or saline was delivered 45 min after injury. Animals receiving naloxone recovered blood pressure rapidly and showed improved forelimb and hindlimb function 3 weeks after the injury. The authors inferred that improved SCBF was the therapeutic mechanism [91]. Further animal studies showed a reduction in ischemia, preserving SCBF and SSEPs [108, 349]. Naloxone also reduced superoxide formation by reactive microglia and antagonized dynorphin A, an endogenous opioid capable of inducing hindlimb paralysis [90], and reestablished normal extracellular calcium levels after SCI in dogs [308]. However, other researchers were unable to verify naloxone mediated improvements on SCBF in rodents with clip compression injury [335]. A small human dose-escalation trial recruited 29 patients and did not show statistical significance in recovery, but had a trend toward SSEP improvements and motor recovery in patients receiving high doses of naloxone (200 mg/m^2 loading dose followed by 150 mg/m^2/h for 23 h infusion) [107]. There were no serious adverse events except increased pain perception in subjects who had additional injuries such as limb fractures and who were neurologically incomplete. In 1990, naloxone was included as one of the NASCIS II trial arms (5.4 mg/kg loading bolus and 4 mg/kg/h infusion for 23 h) along with MPSS and placebo. No statistically significant evidence of improvement in motor or sensory function was detected [36, 37]. As with many other potential neuroprotectants, it's hard to predict the therapeutic window in humans, when the effective window in animals is brief, e.g. 30–60 min. There is a tendency to extrapolate that the window will be longer in humans, but the arguments for this are not persuasive, and efforts to provide the earliest possible safe delivery are needed if neuroprotection is to be effective.

20.3.8 Gacyclidine

Gacyclidine (GK-11 Beaufour-Ipsen Pharmaceutical, Les Ulis, France) is a noncompetitive NMDA receptor antagonist with neuroprotective properties including prevention of glutamate-induced neuronal cell death [82] and stabilization of synaptic currents [332]. Efficacy in SCI animal models was shown in dose-response studies indicating increased functional recovery, reduction in cystic cavitation and astrogliosis [103], higher SSEP amplitudes [115], and an optimal therapeutic window when administered within 30 min of injury [154]. In 1999 a phase II randomized, double-blind, placebo-controlled clinical trial in France was completed; 280 patients were enrolled to receive escalating doses of 0.005, 0.01, and 0.02 mg/kg of GK-11 via IV infusion within 2 h of injury with a second dose within the next 4 h. The analysis showed a nonsignificant trend for a benefit at 30 days in incomplete subjects with cervical injury receiving 0.2 mg/kg. However, this was not evident over placebo at the 1-year follow-up. This study remarkably initiated a neuroprotective strategy within 2 h of injury [319, 320]. Further SCI studies with GK-11 have not apparently been pursued.

20.3.9 Thyrotropin-Releasing Hormone (TRH)

TRH, a tripeptide produced by the hypothalamus, was found to have anti-inflammatory, antioxidant, and membrane-stabilizing properties following SCI [236]. It also became of interest due to its action as an *opiate antagonist* [156]. Faden and colleagues first tested the effects of TRH compared to dexamethasone in a cat contusion model as an alternative to naloxone. TRH is a partial opiate antagonist and thus has less analgesic blocking properties than naloxone. Blockade of analgesia was a concern in the clinical use of naloxone in acute SCI. Higher scores in forelimb, hindlimb, and total functional outcomes were found in animals treated with TRH ($p < 0.01$) [92]. Other properties attributed to TRH from animal experiments include a dose-dependent reduction of leukotriene D4 [105], decreased intracellular pH, tissue cations and edema after trauma [94], increased CNS blood flow [181], excitotoxin antagonizing properties [263], and greater efficacy versus MPSS in tissue sparing [21]. In 1995, results of a small clinical trial for TRH were published by Pitts and colleagues; 20 patients were included in the trial and admitted within 12 h of injury to be randomized to receive TRH (0.2 mg/kg bolus continued by a 0.2 mg/kg/h infusion for additional 6 h) or placebo; both groups included complete and incomplete patients. The analysis took place using NASCIS and Sunnybrook scores at 1, 3, and 7 days and 1, 4, and 12 months post-SCI. The authors report higher motor (58.8 ± 11.9 versus 36.7 ± 23.5 placebo) and sensory (84.5 ± 4.1 versus 55.7 ± 22.7 placebo) scores in incomplete patients at the 4-month evaluation. Although the differences are statistically significant, the data was interpreted as not definitive due to the small sample size. Further, an important number of patients were lost for the 12-month follow-up, and data could not be considered to be informative for this timepoint. Additionally, there were no discernible effects in the complete SCI cohorts [251]. TRH as a neuroprotectant remains an open question.

20.3.10 Nimodipine

The dihydropyridine calcium channel blocker nimodipine has established clinical efficacy for the prevention of vasospasm after subarachnoid hemorrhage ([209, 249]). As raised intracellular calcium levels are damaging to cells affected by SCI [346], it is logical to test drugs that can block calcium channels. Following SCI in experimental animal models, it was found that administration of nimodipine lead to vascular dilation and reduction of blood pressure [140] unless combined with adrenaline [135] to increase adrenergic tone, in which case SCBF could be improved at the site of injury. Further experiments could not verify improvement in SCBF or electrophysiological conduction for either nimodipine or MPSS monotherapy [162, 268]; nimodipine was tested in a human clinical trial in France [247], involving 48 paraplegic and 58 tetraplegic patients randomized to receive: nimodipine (0.015 mg/kg/h for 2 h and 0.03 mg/kg/h infusion for 7 days), MPSS (as per NASCIS II protocol), both, or placebo. One hundred patients were available for the 1-year evaluation. Neurologic improvements were attributed to the natural evolution of the injury with no differences found in any group as compared to the placebo-treated group; the authors additionally reported no benefit from early decompression (8 h post-SCI) in a cohort of 49 patients.

20.4 Experimental Pharmacological Strategies

We now consider therapeutics that have considerable experimental data from animal studies but have not been tested clinically in SCI.

20.4.1 Erythropoietin

Erythropoietin (EPO) is a cytokine glycoprotein hormone produced by the kidney of adults that regulates red cell formation. EPO and its receptor (EPO-R) are expressed in neural tissues, especially neurons and glial cells [68, 77]. In the 1990s it was reported that EPO could reduce apoptosis in a stroke model [269] and that recombinant EPO improved endothelial survival and repair in the ischemic penumbra [208]. EPO and EPO-R are upregulated in the ischemic penumbra by a hypoxemia-inducible factor (HIF) [292]. After further preclinical testing, EPO was translated in clinical trials of ischemia due to stroke [86, 87] and vasospasm after subarachnoid hemorrhage [329]. Clinical efficacy in cerebral ischemia remains unclear [296], and concerns have been raised about the safety of coadministration of t-PA and EPO [356]. In a model of spinal cord ischemia, the immediate administration of EPO, during reperfusion, after 20 min of aortic occlusion, spared ventral motor neurons in a dose-dependent manner [50]. Injection of single doses of intraperitoneal EPO, 1-h post-contusion or clip SCI, was associated with motor recovery and reduced injury sizes [127]. In an NIH-sponsored independent replication study of these reported EPO effects, no differences in locomotor recovery were found

[250], although there was a nonsignificant trend for epicenter tissue sparing. A difference in apoptosis was not assessed, but reported in the index study and other experimental studies of EPO, and could have provided a signal of biological effect. An additional study using the EPO derivative, darbepoetin, could not reproduce the therapeutic effects reported by Gorio et al. [225]. Numerous mechanisms of activity of EPO have been reported such as reduced inflammation by attenuation of IL-6 [4] release and attenuation of astrogliosis with reduction of phosphacan/RPTPζ/β [334]. Recent studies have shown that methylprednisolone prevents oligodendrocyte (but not neuronal) excitotoxin-mediated apoptotic cell death by causing glucocorticoid receptor and HIF-1-α/1-β to bind to the EPO promotor leading to its expression and upregulation of antiapoptotic Bcl-xL gene expression. This level of complexity indicates why it is easy for therapeutics trials to fail without robust iterative preclinical support as well as biomarkers of therapeutics activity. Failures to replicate preclinical studies do not necessarily mean that the therapeutic is ineffective but do suggest that the efficacy is lower than the index study. An endogenously active molecule such as EPO can be predicted to have multiple actions. Recently, two small clinical studies have been reported in which EPO was compared to MPSS. A modest superiority of EPO was reported [6, 64]. It is important that in larger studies EPO will be compared to placebo as there is increasing information that MPSS may worsen the transient immune deficiency associated with SCI [180].

20.4.2 Anti-CD11d

Inflammation is a prominent cause of secondary injury; SCI evokes substantially more potent neuroinflammation than brain injury [357] and elicits a multi-organ systemic reaction [45]. Post-SCI systemic inflammation includes damage to the lung, kidney [129], and liver [109, 273]. The extent of liver inflammation was greater for T4 as compared to T12 injuries. Other data supports that post-SCI immune dysfunction is spinal-level dependent and corresponds to the degree of loss of sympathetic regulation of the immune system [277]. The term "leukocyte" refers to all circulating white blood cells. Those known to be important in SCI are neutrophils, monocytes, and lymphocytes. Both leukocytes and monocytes independently contribute to injury propagation [201]. SCI leads to endothelial injury and the presentation of selectins and vascular cell adhesion protein-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) which regulate monocyte rolling, stabilization, and diapedesis from the blood vessel into the perivascular space. Leukocytes express cell surface integrins that bind to the cell adhesion molecules (CAMs) and have roles both in endothelial adhesion and migration through vessel walls and tissue. This process mainly occurs in *postcapillary venules* where the shear forces are lower, fostering adhesion. *Proof-of-concept studies* have sought to *deplete* circulating white cells or to *block* their exit from the vascular space into spinal cord tissue. Depletion of circulating macrophages was associated with tissue preservation [30], improved locomotor outcomes [254], and reductions in fibrotic scar formation [362]. However, other studies that depleted neutrophils in mice found a worse outcome [307] indicating the

complexity of the effects of inflammation after SCI and the limitations of simplistic approaches such as generalized blocking. Another study found that certain populations of macrophages that migrate into the injury site after SCI are neuroprotective [282] and that depletion of CD11-positive monocytes worsened neurological outcome. Others have shown that the persistence of macrophages is associated with axonal dieback [157]. Thus, the associated biology is complex.

Antibodies have been tested as therapeutics; those against P-selectin partially blocked neutrophil spinal tissue entry with reduced tissue myeloperoxidase activity and improved early locomotor function post-SCI [323]. CD11d (αDβ2 integrin) is expressed by monocytes and leukocytes and is involved in leukocyte activation and endothelial adhesion through interaction with its ligands ICAM-1 and VCAM-1 [28]. Mabon and colleagues developed a monoclonal antibody against αD to be administered intravenously in a transection rat model: 24 h before transection and 2 and 24 after transection (1 mg/kg dose). Two of the three anti-αD tested antibodies (228H and 236L) caused a 65 % reduction of macrophages in the injury site and one (236L) a 43 % reduction in neutrophils [219]. Later studies using a clip compression model assessed the mechanisms by which anti-CD11d was beneficial after SCI finding a reduction in myeloperoxidase (MPO) activity, thiobarbituric acid reactive substances (TBARS), and attenuated inducible nitric oxide synthase (iNOS) expression [16]. In another study, the reduction of reactive oxygen and nitrogen species was assessed demonstrating a decrease in COX-2 and 8-OHdG (a marker of RNA and DNA oxidation) expression, a reduction in protein carbonyl formation, and an increase in APE/Ref-1 (involved in repair of apurinic/apyrimidinic sites) formation [15]. Studies comparing anti-CD11d to MPSS showed both treatments increased neurofilament sparing, but myelin sparing was less with MPSS, with no differences in the neurological outcomes of the anti-CD11d+MPSS versus the MPSS group [339], but with significant differences in BBB scores when plotted against an anti-CD11d cohort reported by the researchers group in a previous publication [131]. There was no additive effect of MPSS; the anti-CD11d group had smaller lesion areas [130], increased serotoninergic fiber density below the injuries, and reduced allodynia in the dorsal trunk and hind paws [237].

Regarding therapeutic window, the treatment could be delayed until 6 h post-injury with improved BBB scores and decreased autonomic dysreflexia [79]. A subsequent study examined the relative expression of the key ligands on monocytes in normal adult humans versus those with general trauma and those with SCI. Higher densities of α4 and CD11d were found on neutrophils and monocytes after SCI but not after general trauma [13]. Anti-CD11d therapy also attenuated the systemic inflammatory response, with reduced inflammatory neutrophil and macrophage infiltration in lungs and kidneys [14]; this response was also evident after treatment with anti-α4β1 antibody [17]. Neuroprotective effects of anti-CD11d were found after SCI in mice [120]. An independent replication of the results previously reported was sponsored by the NIH to validate the results, but only nonsignificant trends on motor recovery and tissue sparing with the anti-CD11d treatments were found [161]. Another recent study used a different strategy to deplete both monocytes and neutrophils and found that the optimum protection required both be

reduced [201]. Although there is substantial data in support of anti-CD11d antibody treatment post-SCI, no clinical trials have yet been announced. In stroke, an extensive study of an anti-ICAM antibody indicated the treatment worsened outcome [88] possibly due to the immunological effects of the use of murine antibody. Leukarrest, a humanized, anti- CD11b/18 antibody, reduced infarct size in animal models. However, no benefit was found in a phase III clinical trial [20].

20.4.3 Polyethylene Glycol

Polyethylene glycol (PEG) is a simple polymer with established safety in the pharmaceutical industry. It is a membrane fusogen, used, for example, in the generation of hybridoma cells to produce monoclonal antibodies [179]. Experiments conducted in a guinea pig severe spinal cord compression model showed that a solution of PEG in distilled water applied by pressure injection in the injury site repaired axons such that compound action potential conduction through the lesion recovered [283] and there was progressive recovery of the cutaneous trunci muscle reflex (CMT) [33]. Subcutaneous delivery of PEG was assessed and apparently selectively targeted the contused areas within the spinal cord with beneficial effects at a 6-h therapeutic window [32]. Histological three-dimensional reconstructions showed higher volumes of intact parenchyma and reduction of cystic cavitation in animals receiving PEG treatment directly over the spinal cord, immediately, or with a delay of 7 h after compression [84]. ROS elevation and lipid peroxidation also were inhibited by PEG [215]. A pilot study in dogs with SCI tested the intravenous delivery of the polymer at 30 % w/w in saline at 2 ml/kg within 72 h post-injury with a second delivery 4–6 h later. The authors reported no adverse events and an ambulation recovery in 68 % of treated dogs versus 25 % of controls and proprioception recovery in 42 % of treated versus 4 % of controls [197]. Mechanistic studies have indicated that PEG stabilizes mitochondrial calcium flux and reduces cytochrome-C release [211, 216, 217]. Additional rodent studies showed that animals treated within 15 min or 6 h with IV PEG had enhanced BBB scores and reduced mechanical allodynia up to a 6-week evaluation timepoint. When PEG and $MgSO_4$ were combined, the additive effect was no greater than either single treatment [80]. An independent study conducted by Baptiste, Fehlings, and colleagues confirmed tissue-preserving effects of IV PEG 30 % delivered 15 min after 35-g clip compression. An increase in retrogradely labeled brainstem axons and a reduction in apoptosis of epicenter cells were observed. The small effects on locomotor scores left the authors to question if the therapeutic impact justified translation as a single treatment for SCI trials [18]. In a rodent contusion model, Kwon and colleagues assessed combinations of PEG with magnesium and found that PEG alone did not significantly improve open field locomotion up to 6 weeks post-treatment [186, 188]. More recent experiments performed by Borgens and colleagues include the incorporation of PEG with silica nanoparticles [55, 57] or micelles such as monomethoxy poly(ethylene glycol)-poly(d,L-lactic acid) di-block copolymer. Apparently, these formulations allow a more precise targeting to damaged neural tissue and a greater repair effect. It has been reported that PEG is superior to Matrigel,

or alginate hydrogel in supporting regeneration after complete spinal transection [89]. So far PEG has not been studied in a human SCI clinical trial other than in combination with magnesium.

20.4.4 Estrogen

Clinical and experimental studies indicate that females tend to exhibit greater neurological recovery than males after equivalent spinal cord injuries [69, 96, 291], implicating a possible role for estrogen as a neuroprotectant. Estrogen has been shown to reduce leukocyte adhesion and infiltration [327] and attenuate microglial superoxide release and phagocytic activity [43]. In vitro experiments showed protection of hippocampal neurons against glucose deprivation, glutamate, $FeSO_4$, and amyloid beta-peptide (Aβ) toxicity [126]. In 2004, Yune and colleagues reported neurological outcomes after a *mild* NYU contusion impact (12.5 g/cm) in male rats. 17β-estradiol was administered IV at 3, 100, or 300 μg/kg^2 hours *prior* to injury or 100 μg/kg immediately post-injury. For the pre-administered doses, 100 μg/kg had the largest effect. After 30 days the BBB scores for animals in the 100 μg/kg cohort were 18.3 ± 0.6 ($p < 0.001$) versus 15 ± 1 in vehicle only. The lesion area was reduced, 2.06 ± 0.2 mm^2 ($p < 0.05$) versus 2.5 ± 0.3 mm^2, as was apoptosis 50 ± 5 versus 134 ± 8 ($p < 0.001$) TUNEL + ve, caspase-3 activation 5.7 ± 0.81 versus 9.8 ± 0.95, $p < 0.001$, and increased BCL-2 and BCL-X labeling. In another study cohort, the steroid was administered immediately after injury, and a substantial effect on BBB at 30 days was observed [351]. These data strongly supported a neuroprotective potential of 17β-estradiol in SCI but lacked clinical relevance since a therapeutic window was not assessed. Sribnick and colleagues reported in 2005 a male rat contusion model using higher doses of 17β-estradiol (4 mg/kg administered 15 min and 24 h post-injury IV). With a short survival of 48 h, there was reduction in tissue edema, infiltration of microglia and macrophages in the injury site and caudal penumbra, and attenuation of myelin loss in the injury site [300]. Further experiments by the group using the same methodology demonstrated attenuation in degradation of 68 kD neurofilament, reduction in calpain protein levels, decrease in cytochrome-C levels, and neuronal apoptosis in estrogen-treated animals [298, 299].

The issue of a neuroprotective effect of estrogen replacement in an SCI model of pre- and postmenopause tested the effect of preimplantation of a 17β-estradiol capsule (180 g/ml) 1 week before injury followed by a 0.5 mm forceps crush at T8/9. Neuroprotection was observed in both pre- and postmenopausal (ovariectomized) rats with improved white matter sparing, anterior horn cell preservation, reduced apoptosis, and higher BBB scores, although premenopausal rats (non-ovariectomized) had higher scores than estrogen treated. There was no effect on the manually voided urine volumes by 21 days post-injury [51]. Testing in the mouse species using a T10-controlled compression confirmed that females had substantially superior outcomes to males on the mouse BBB score [96].

A well-designed study tackled the issue of sex differences by comparing males to ovariectomized females with both implanted with a control, low-dose or

high-dose estrogen-releasing capsule (low-dose 180 μg/ml, high-dose 1 mg/ml) 7 days prior to a moderate 150-kilodyne T10 injury. The serum estrogen levels were measured and reflected the dose delivery from the implanted capsule. The 21-day post-injury BBB was not significantly improved over the non-estrogen control in male or female rats. Injury length and tissue sparing favored females over males, but this effect was deemed not to be attributable to estrogen delivery. The authors concluded that no effect of estrogen delivery on SCI outcome was evident [318].

A mouse study used a 24-g clip compression at T6/7 with the subcutaneous delivery of 300–500 μg/kg of E2 before and after injury. They reported that estrogen reduced neutrophil infiltration, expression of myeloperoxidase, iNOS, nitrotyrosine, cyclooxygenase-2 (COX2), BAX, and apoptosis demonstrated by terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL), TNF-α, IL-6, and IL-1β. The effects were abolished by a coadministered estrogen receptor antagonist [67]. Neuronal antiapoptotic effects and reduction in microglial activation were found in a rat contusion model even at small doses of 5 or 10 μg/kg [270]. A recent study showed that immediate post-T10 NYU 25 g/cm contusion delivery of 300 μg/kg of E2 protected the blood-brain barrier, with reduced hemorrhage, matrix metallopeptidase 9 (MMP9) and sulfonylurea receptor1 (Sur1) Transient receptor potential cation channel subfamily M member 4 (TrpM4) expression, reduced neutrophil and macrophage migration, and reduced inflammatory cytokine expression in male rats [199]. If estrogen is to be considered a potential neuroprotectant, there is a need for studies to establish a therapeutic window and rigorously evaluate safety.

20.4.5 Progesterone

Progesterone (PRO) is primarily known as female sex hormone produced by the ovary. However, PRO, like estrogen, has pleiotropic effects and is an important neurosteroid that is locally produced in the brain and has a key role in myelination [275]. PRO has been demonstrated to reduce inflammation and attenuate neuronal and glial loss [66, 303] in traumatic brain injury (TBI). Thomas and colleagues first reported testing progesterone therapy for SCI in a standard T9 25 g/cm NYU, contusion model. Adult male rats received 4 mg/kg of PRO intraperitoneally for 5 days beginning 30 min after injury, and significant improvements in BBB scores and white matter preservation were reported at the 6-week timepoint [328]. Fee et al. attempted to replicate some elements of the Thomas study but used a milder injury, 150-kilodyne T10 Infinite Horizon, and both male and female rats. PRO 4 mg/kg or 8 mg/kg was delivered at 30 min and 6 h post-injury and continued for either 5 or 14 days. As with the Kentucky group's parallel study of estrogen [318], no gender differences were observed with PRO treatment after SCI. Regarding tissue sparing and BBB testing, there were no apparent differences effects between PRO and control at the 21-day assessment timepoint [98].

A recently published study evaluated PRO in male rats with a T8 200-kilodyne Infinite Horizon injury. Animals were randomized to receive subcutaneous injections of 16 mg/kg/day PRO or castor oil, starting 1 h post-injury and continued for 60 days until sacrifice. Outcome assessments included Catwalk automated gait

analysis and stereological histological techniques. The authors found a benefit to PRO with improved BBB scores (mean 14 versus 11 in controls), subscores, and gait elements such as a reduced base of support and improved stride length and swing phase. Ex vivo MRI analysis found significant differences in injury volumes and spared tissue indicating a positive effect of PRO. There was a substantial sparing of white matter above and below the lesion epicenter. The number of CC1 immunopositive oligodendroglia, myelin basic protein (MBP)-positive segments, and neurofilament-labeled axonal profiles was increased in PRO-treated rats [114].

Other studies using a variety of injury models have identified several putative mechanisms of PRO effect. Reactive astrocytes in SCI were reduced in the injury site by doses of 4 mg/kg at 1, 24, 48, and 72 h post-T10 transection in male rats [193]. The same treatment paradigm restored the expression of the α3 and β1 regulatory subunits of NA-K-ATPase with further upregulation of growth-associated protein (GAP-43) in ventral horn motoneurons [190], produced upregulation of NG2-positive cells [70], enhanced brain derived neurotrophic factor (BDNF) immunoreactivity, and prevented chromatolytic degeneration in motoneurons with preservation of the cytoskeletal component identified by MAP2 [124, 125]. Regarding potential effects on myelination, a dose of 16 mg/kg started 3 h post-injury and continued until sacrifice increased the expression of mRNA and MBP and increased mRNA and protein expression for oligodendrocyte differentiation factors Olig2 and Nkx2.2 at 3 days. If treatment was continued until 21 days, markers of mature myelin recovery included reduced oligodendrocyte precursor cells and increased oligodendrocyte mRNA expression of proteolipid protein (PLP) and Olig1 [191]. In a different study, inhibition of astrocyte and microglia/macrophage proliferation and activation was found [192]. Currently, there is no indication for the use of progesterone in the clinic as a neuroprotective for SCI, and further study of a therapeutic window in contusion injury would be important.

20.4.6 Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

Another important class of anti-inflammatory drugs for which there is extensive clinical experience are NSAIDs that inhibit cyclooxygenase 1 and 2 and thus the production of eicosanoids from arachidonic acid. Their activity reduces the production of prostaglandins, thromboxanes, and leukotrienes. Pre-injury delivery of indomethacin substantially reduced tissue prostaglandin levels in a feline SCI model [172]. In another feline SCI study, a triple combination treatment of indomethacin, heparin, and prostacyclin (PGI_2) one and three hours *post*-weight-drop contusion was compared to naloxone and saline control. The combination including indomethacin showed similar Tarlov locomotor scores to those animals receiving naloxone, with both superior to saline control [144]. Fujita and colleagues found that aspirin pretreatment (5–50 mg/kg) also reduced lipid peroxidation and decreased prostaglandin production [111]. A dual lipoxygenase/cyclooxygenase inhibitor BW755C administered prior to trauma decreased the accumulation of thromboxane B_2, improving neurological recovery in rat contusion model, but the same effect was not achieved when applied post-injury [93].

Further experimental studies conducted during the 1990s assessed the effects of indomethacin after SCI. These showed neurological improvement with reduced tissue injury in rats (2 mg/kg post-injury + every 24 h during 7 days) [290], decreased edema and attenuated motor evoked potential changes (10 mg/kg 30 min pre-injury) [342], and ultrastructural demonstration of decreased edema (10 mg/kg 30 min pre-injury) [279].

A lack of effect of indomethacin was also reported: no locomotor improvement unless combined with pregnenolone and lipopolysaccharide (0.2 mg after injury + every 24h during 21 days) [138], increased lipid peroxidation when compared to saline treatment (3 mg/kg after injury) [139], and increased levels of MPO and TNF with greater motor deficit and histological damage (5, 10, 20 mg/kg 1 h pre-injury) [149]. The study by Guth and colleagues is notable as this was a combination selected to increase monocyte cytokine secretion using lipopolysaccharide, to provide anti-inflammatory steroid activity with pregnenolone, and to block prostaglandin production with indomethacin. Multiple pair-wise and triple combinations were tested that included aspirin and dehydroepiandrosteron (DHEAS) as alternate anti-inflammatory controls. The injury was created at T8 using 2 s of jeweler's forceps compression. Only indomethacin, pregnenolone, and lipopolysaccharide (LPS) combined were associated with substantial locomotor recovery and reduction in the lesion area. Eighteen years later, an National Institute of Neurological Disorders and Stroke (NINDS) supported replication was reported by the team at Ohio State. An attempt was made to replicate the forceps compression injury, and a sustained release pellet (lipopolysaccharide 0.2 mg, indomethacin 0.16 mg, pregnenolone 150 mg) was inserted into tissue adjacent to the laminectomy, and the animals survived for 28 days. An effect of the triple combination was found on white matter preservation, preserved neurofilament area, and axon density. No effect, however, was detected in the BBB scores, subscores, or imputed Tarlov scores, with assessments up to 28 days post-injury [256]. In a brief rebuttal, Dr. Guth pointed out that the control animals in the replication study showed more spontaneous recovery than in the original study making it difficult to show a difference in locomotor recovery [137].

A very interesting property of some NSAIDs is the ability to *reduce RhoA activation* after SCI. In the first study, indomethacin was injected at 2 mg/kg/day IP after a T8 dorsal over hemisection. The tissue was examined on day 3 for sources of RhoA activity. The treated rats showed a decrease in RhoA expression in microglia/macrophages, astrocytes, and neutrophils with an increase in GAP-43 positive neurites [276]. In a second experiment, the impact of ibuprofen versus naproxen on RhoA activation, axonal growth, and locomotor recovery was assessed, with drugs delivered for 28 days via an Alzet minipump, ibuprofen (60 mg/kg/day), naproxen (50 mg/kg/day), or saline. The treatment was initiated immediately after an extensive dorsal T6/7 oversection, or *7 days after* a T8/9 moderate NYU contusion injury. In vitro assays showed inhibition of RhoA activation by ibuprofen and indomethacin but not naprosyn. Interestingly, the inhibition was of similar potency to C3 transferase (see Cethrin above). At 5–7 days post-contusion, RhoA was markedly reduced in spinal

cord tissue by ibuprofen but not naprosyn. In the sharp section, animals with immediate delivery CST axon growth distal to the lesion were found in anterogradely traced animals that received ibuprofen but not naprosyn or control. In the contusion animals with treatment initiated at 7 days post-SCI, improved serotonergic axonal growth below the injury level was observed. In both injury paradigms, the BBB score at 42 days was higher in the ibuprofen-treated animals [110]. A subsequent study further examined these issues using both in vitro assays and rat experiments. A T7/8 25 g/cm NYU contusion was created and *3 days after* injury an Alzet minipump implanted to deliver 70 mg/kg/day ibuprofen, 25 mg/kg/day naproxen, or PBS. The rats survived either 2 or 6.5 weeks. In a separate experiment, mice underwent T8 spinal cord transection and were simultaneously implanted with minipumps to deliver either 35 or 70 mg/kg/day of ibuprofen for 28 days. The in vitro studies showed a dose-dependent reduction in MAG-mediated inhibition. Both weight-bearing status and BBB scores were increasing in ibuprofen- but not naprosyn-treated animals up to 50 days post-injury, and Rho activation was reduced in spinal cord tissue. Tissue preservation was significantly better in ibuprofen as compared to naprosyn- and PBS-treated animals at 2- and 4-week timepoints. There was extensive sprouting of the CST rostral to the contusion site in contused rats that received ibuprofen, and the terminations of the tract were not retracted from the injury as is usually seen and was observed in the naprosyn- and PBS-treated animals. No distal CST regeneration, however, was observed. Six weeks post-injury, ibuprofen-treated rats showed substantially more serotonergic fiber density distal to the contusion site, apparently due to regenerative sprouting from preserved processes. In completely transected mice, regenerative growth of serotonergic fibers through the transection and distally was observed together with improvements in the Basso Mouse Scale for Locomotion (BMS) [337]. The Fu et al. study was selected for replication by the Facilities of Research Excellence—Spinal Cord Injury (FORE-SCI) NIH group, conducted at UC Irvine. Despite consultation with the senior author, Dr. Li, of the index study, no aspect of the original results could be confirmed other than the suppression of Rho activation by ibuprofen [280]. A recently reported study assessed ibuprofen in combination with C16, a vascular preserving peptide; ghrelin, a neuroprotective gastric hormone; and ketogenic diet in a C5 hemicontusion paradigm. No effects were apparent using rodent upper extremity functional assessments and light microscopy-based tissue sparing analysis [309].

Selective inhibitors of inducible cyclooxygenase 2 were studied. Following a 25-g/cm NYU impact, celebocid (3 mg/kg) was delivered PO 20 min post-injury. The levels of prostaglandin E2 (PGE2) and thromboxane B2 (TxB2) were reduced by the drug at 4 and 24 h post-injury [264]. A single injection of NS-398 5 mg/kg delivered 15 min prior to a 12.5 g/cm NYU T13 also decreased prostaglandin E2 (PGE2), increased spared tissue, improved BBB scores 14–28 days post-SCI, and reduced mechanical allodynia and thermal hyperalgesia [141]. It is notable that in this injury model, the pain behaviors are found in forelimbs above the injury and the hindlimbs below the injury. This indicates that CNS reorganization after SCI occurs not only at and below the injury level.

20.4.7 Glibenclamide

Glibenclamide, known as glyburide in the USA, is a well-known sulfonylurea developed in the 1960s for the oral treatment of type 2 diabetes [226]. Due to its ability to close K_{ATP} channels (pore formed by subunits SUR1 and Kir6.2), it stimulates the secretion of insulin by β islet cells [10]. Interest in its potential for SCI was due to the identification of an upregulation of the SUR1 subunit in a characteristic phenomenon of TBI and SCI known as progressive hemorrhagic necrosis (PHN) [285], which is described as a progressively confluent petechial hemorrhage adjacent to the injury sites [12]. The mechanism of PHN is not yet known, but it is understood to be a progressive capillary blocking due to mechanical stress after secondary injury [325] or leukocyte infiltration [175].

In a rat cervical hemicontusion model, SUR1 was identified to be upregulated in endothelial cells and neurons surrounding necrotic injuries, beginning its expression in the epicenter at 6 h post-injury and expanding to the injury rim and adjacent tissues within 24 h. The delivery of glibenclamide via infusion pump (200 ng/h) after 2–3 min of injury resulted in a threefold reduction of injury volumes; decreased intraspinal hemorrhage at 6, 12, and 24 h; and significant neurobehavioral improvement in BBB scores and inclined plane testing at 1, 3, and 7 days post-injury [288]. An NIH-sponsored independent replication study was carefully conducted. When initial data failed to replicate the index study of Simard and colleagues, extensive efforts were made to ensure that the same injury methodology was being employed. When this was achieved, an effect of glibenclamide could be verified [255, 256]. This experience underscores the importance of exact attention to detail in replication studies. In a subsequent study, the effect of glibenclamide was assessed in two hemicontusion injury methods. In the more extensive injury, small but significant effects of glibenclamide on behavioral outcomes and tissue sparing were observed [287]. It should be noted, however, that the drug was administered within 5 min of injury. In another study, glibenclamide was compared to riluzole with administration performed either immediately after unilateral C7 injury or at the 3-h timepoint. Unfortunately, nearly all of the control animals died resulting in a comparison between the two drugs but without a vehicle comparison. Glibenclamide resulted in superior tissue preservation, grip strength, rotarod stability, and rearing [289]. A subsequent study assessed the effects of glibenclamide on the progression of hemorrhagic injury volume using MRI [286]. Glibenclamide appears as a promising neuroprotective approach for SCI, but further studies in more severe lesion models and with additional timepoints of drug delivery should be conducted to compare its effects to other agents in rodent models. Clinical trials in stroke and TBI have been initiated.

20.4.8 Thiazolidinediones

Thiazolidinediones (TZDs) are used in the treatment of type 2 diabetes and are agonists of the peroxisome proliferator-activated receptors gamma (PPARγ). These are

"nuclear receptor" DNA-binding compounds that regulate fatty acid storage and hepatic glucose metabolism [170]. A model assessing factors involved in the macrophage-mediated expansion of SCI cavity size included testing of ciglitazone (the prototypical TZD) with an in vitro cavity model of cultured astrocytes and activated macrophages. Ciglitazone potently reduced the increase in the areas of culture cavities mediated by zymogen-activated macrophages [106]. Later with the development of pioglitazone (PGZ) which crosses the blood-brain barrier [317], a rat contusion model compared high (10 mg/kg) versus low (1 mg/kg) doses of the TZD, started 15 min post-injury and maintained BID for 7 days. The differences in BBB scores were not significant with a positive trend for the high-dose group (15.4 ± 1.1 versus 13.3 ± 1.3 in controls), but differences were more evident in subscores (toe clearance, coordination, parallel paw position). The high-dose group had improvements in spared white and gray matter areas rostral to the epicenter and better neuronal counts rostral and caudal to the epicenter; no differences were observed in caspase-3 immunoreactivity or macrophage detection [232]. A concurrent study by a different laboratory compared the treatment effects of PGZ and rosiglitazone (RGZ) (0.5, 1.5, 3 mg/kg at different timepoints) and the PPARγ antagonist GW9662 (2 mg/kg 1 h prior to any TZD injection). Both TZDs decreased lesion areas (57 % RGZ, 64 % PGZ) significantly and increased neuronal survival; decreased astrogliosis, microglial activation, myelin loss, induction of inflammatory genes; and enhanced induction of neuroprotective heat-shock proteins and antioxidants, with improved BBB scores (final scores at day 7 PGZ 12.9 ± 1.4, RGZ 12.2 ± 1.1, vehicle 8.9 ± 0.7); these effects were inhibited by the GW9662 treatment. The therapeutic window of intervention indicated no significant effects of a delay in administration >2 h and similar effects with 3 or 1.5 mg doses with no effects at 0.5 mg; additionally PGZ exhibited a decrease in thermal hyperalgesia [244]. In other studies, intrathecal delivery of RGZ decreased neuropathic pain [59], and similar effects were observed with oral administration of PGZ [220]. Anti-inflammatory effects of RGZ (reduction of TNF-α, IL-β, myeloperoxidase activity) were evident in a clip compression model [358], and a comparison between MPSS and RGZ demonstrated greater increased neurotrophin expression and improved early recovery in the RGZ group [359]. There are no published studies in SCI to disprove the effects of TZD treatment, and having two studies performed by independent groups with similar results within the same year is strong evidence. There are additional reports from Chinese studies [169, 207, 345]. It may be valuable to test TZD in a large animal contusion model.

20.4.9 Atorvastatin

Atorvastatin and statins, in general, are competitive inhibitors of the 3-hydroxy-3methylglutarylcoenzymeA (HMG-CoA) reductase which catalyzes the reduction of HMG-CoA to mevalonate, inhibiting the synthesis of hepatic cholesterol, increasing the uptake of low density lipoprotein (LDL), reducing triglyceride levels, and increasing high density lipoprotein (HDL) levels. Statins have anti-inflammatory effects, in astrocyte and microglial cell cultures exposed to LPS. Lovastatin blocked the

expression of inducible nitric oxide synthase (NOS) and TNF-α, IL-1β, and IL-6 [241]. In MBP-induced experimental models of experimental autoimmune encephalomyelitis (EAE) in Lewis rats, lovastatin was found to reduce the numbers of infiltrating mononuclear cells by downregulating the ICAM ligand Lymphocyte function-associated antigen-1 (LFA-1), to reduce demyelination, and to reverse paralysis [301]. In further EAE studies, atorvastatin was found to increase a Th2 over Th1 cytokine and cellular phenotype [350]. The studies in SCI by Pannu and colleagues used a rat contusion model with an oral atorvastatin dose of 5 mg/kg/day until sacrifice (15 days). All groups in the study received a pretreatment regimen of atorvastatin for 7 days; animals that continued on statins exhibited higher BBB scores that started to deviate significantly from the vehicle group by day 3 (6.57 ± 0.55 vs 0.166 ± 0.33) and showed near-normal scores by day 15 (19.13 ± 0.53 vs 9.04 ± 1.22). Statin-treated animals had reduced post-injury levels of TNF-α and IL-1β, decreased infiltration of ED-1 macrophages, attenuated neuron, and oligodendrocyte apoptosis demonstrated by TUNEL assay, reduced gliosis, tissue necrosis, and demyelination [242]. Evaluation of the therapeutic window was subsequently assessed by not pretreating and randomizing contused animals to start treatment at 2, 4, or 6 h post-injury, with continued drug treatment until sacrifice (42 days). BBB analysis showed much higher scores for all treated groups at 42 days (2h 19.5 ± 1, 4h 19.25 ± 1, 18.5 ± 0.5) versus 10.5 ± 1.5 vehicle control; these results were supported by attenuated necrosis and demyelination; decreased neutrophil and macrophage infiltration; decreased expression of iNOS, TNF-α, and IL-1β; attenuated expression of MMP9 via inhibition of the RhoA/ROCK pathway with preservation of the blood-brain barrier; and reduced neuronal apoptosis [243]. These are remarkable results clearly requiring independent evaluation. A Canadian study assessed the relative effects of simvastatin and atorvastatin as the former is more lipophilic, using oral gavage delivery in saline, fed in chocolate ensure, or purified simvastatin alone administered subcutaneously initiated 2h after injury. The OSU device was used to deliver a 1.5-cm displacement at 300 m/s. In brief, the results failed to show effects that justify clinical translation. There were higher BBB scores in the statin group in one experiment that could not be reproduced in others: white matter tissue sparing showed a nonsignificant trend toward positive effects but did not reach statistical significance (42 ± 6% vs. 34 ± 8% in controls), and the one statistically significant difference was obtained at 3 days comparing the extent of ED1 staining at the injury epicenter [224]. A second Canadian study examined the effect of atorvastatin-administered IP 5 mg/kg 2 h post-SCI for 15d with a 4 week survival. An early reduction in TUNEL labeling and caspase-3 activation was observed, with a statistically significant improvement in BBB score at 4 weeks post-SCI. In conclusion, statins may offer an approach for post-SCI neuroprotection, but additional evidence is needed to resolve inconsistencies in the literature and determine if the cost and effort of a clinical trial is warranted.

20.4.10 Inosine

Inosine is a purine nucleoside found in tRNAs and is a popular athletic supplement. It's metabolism to uric acid has antioxidant effects. One of its earliest uses in neurology was as a component of the drug isoprinosine that was found to have beneficial

immune-modulating properties during viral diseases such as subacute sclerosing panencephalitis [171]. Inosine stimulated axonal outgrowth in retinal ganglion cell cultures [26]. Subsequently, its impact on CST structural plasticity was studied in a rodent model of unilateral pyramidal section. Twenty-four hours after the injury, animals were implanted with minipumps to continuously infuse inosine (10 mM 0.5 μl/h) for 14 days into the non-axotomized sensorimotor cortex. Inosine stimulated the uninjured pyramidal axons below the lesion to extend new collaterals across the midline into denervated areas of the lesioned tract [24]. An upregulation of GAP-43 expression was observed in axons forming new collaterals [25] as is seen in regenerating axons. Mammalian sterile 20-like kinase-3b (Mst3b) activation was specifically linked to inosine stimulated axon outgrowth [165]. Further studies have indicated that Mst3b is an important regulator of axonal growth after injury in both CNS and peripheral nervous system (PNS) neurons [165, 213]. In models of unilateral stroke, intraventricular delivery of inosine [354] did not reduce infarct size but was associated with improved recovery of affected forepaw function, sprouting of CST axons into the denervated tract, and upregulation of genes associated with axonal growth in the uninjured cortex. In a second stroke study, inosine amplified the effects of a coadministered Nogo blocker and was again associated with increased forelimb function [353]. In a rodent T8 dorsal spinal cord hemisection model, the effects of intraventricular (50 mM 0.5 μl/h) and intravenous (8–27 mg/kg/day) inosine delivery were compared. Both delivery methods were associated with significant increases in BBB scores and ladder walking tests. Inosine treatment did not affect lesion size but increased CST sprouting in the cervical spinal cord rostral to the lesion with new synaptic contacts with long propriospinal interneurons that could form novel relays and also was associated with increased serotoninergic immunoreactivity to the lumbar spinal cord below the cord section [176]. In a Chinese study, a single dose of inosine was administered IP at 2, 12, or 24 h after T9 clip compression injury. Epicenter tissue preservation and a reduction in the number of apoptotic cells were detected at 3 days in the 2- and 12-h treatment groups with the 2-h treatment being the best [210]. In another experiment, inosine effects appeared to be enhanced by oscillating field stimulation with regeneration of ascending and descending projections of spinal cord tracts and recovery of the cutaneous trunci muscle reflex in chronic SCI [31]. Continued subcutaneous delivery of inosine started 15 min post-thoracic contusion injury reduced the number of ED-1 positive profiles at the injury site [62]. In 2012, an NIH-sponsored independent replication study of the methodology published by Benowitz in 1999 was reported from UC Irvine. The authors described difficulties with complications and deaths secondary to the pyramidotomy surgeries; nevertheless, after several trials the results failed to confirm that CST axons sprouted across the midline [304, 305]. Sources of possible error in interpreting the histological appearance of CST axons at the midline were discussed. The most recent study testing inosine in SCI reported neuronal survival, tissue sparing, and improved locomotion after oral administration of inosine (1.2 g/kg/day, beginning 2 h post-injury) [185]. In summary, there is substantial evidence for inosine as a promoter of axonal plasticity after injury. Combined with its established use in drugs and as a health supplement, clinical testing may be reasonable if pivotal preclinical studies to assess the route of administration and pharmacokinetics were supportive.

20.4.11 Imatinib

Imatinib a tyrosine kinase antagonist, is one of the most successful cancer drugs ever developed and has fundamentally changed the treatment of chronic myelogenous leukemia. As with other "repurposed" drugs, we have discussed such as minocycline, riluzole, statins, and glibenclamide, there is extensive human experience with dosage and side effects. This experience makes the translation pathway less complicated. Imatinib was shown to preserve blood-brain barrier integrity in a stroke model by inhibiting the activity of the platelet-dervied growth factor (PDGF) α receptor [314]. Furthermore, imatinib is a very illuminating example of disparities between index studies and replication attempts. Potent neuroprotective effects were reported by Abrams et al. in 2012 [2]. The dose was 250 mg/kg given orally 30 min after a thoracic 25 g/cm NYU contusion and continued for 5 days. Several significant functional effects were seen, improved BBB scores, contact placing responses, and a substantial reduction in bladder urine retention after voiding. There was epicenter tissue and neurofilament preservation, reduced numbers of macrophages, astrocyte reactivity, and chondroitin sulfate proteoglycan (CSPG) deposition in the injury region. Blood-barrier integrity was improved with a reduction in albumin leakage. Detectable PDGFR-α and PDGFR-β were reduced at 5 days post-injury, and tight junction protein claudin 5 was better preserved. An NIH-supported replication study failed to reproduce the findings other than the significantly reduced post-void residual bladder volume [281]. A potent rebuttal by the index study authors showed that the replication injury severity was significantly less than that of the index study precluding the ability to demonstrate recovery of weight-supported stepping and creating a ceiling effect for contact placing. Other flaws in the replication were noted as well [1]. In a recently published study, Kjell and colleagues further examined the therapeutic window assessing delivery at 4, 8, and 24 h, continuing for 14 days, after a milder contusion injury that facilitated automatic analysis of coordinated stepping. They used the same dose as the original study 250 mg/kg PO. Effects on the BBB, subscores, and coordination were evident with 4- but not 8- or 24-h delivery [178]. Improved bladder emptying was found at all timepoints as compared to placebo control. A specific peripheral blood profile of cytokine activation was consistent in animals receiving imatinib. In an EAE model of spinal multiple sclerosis (MS), imatinib was shown to markedly attenuate disease by protecting blood-brain barrier integrity, by reducing endothelial expression of molecules mediating the entry of lymphocytes and other inflammatory cells to the tissue, and by promoting the Th2 phenotype in the peripheral immune system [3]. Peripheral IL-4 was markedly increased; IL-4 is an important promoter of Th2 and M2 tissue repair macrophage phenotype. One interesting point the authors do not discuss is that the dose administered to the rats appears far higher than that used for human malignancies, typically a total of 400–800 mg/day in adults [246]. For a typical 70-kg male, 250 mg/kg would be a daily dose of 17,500 mg, 40× higher than the standard cancer dose.

20.5 Conclusions and Final Remarks

Currently, there is no clinically established neuroprotective treatment that has met the standard of showing a prospectively established increment of neurological recovery superior to control, or alternate therapy, in a suitably designed randomized study with acceptable morbidity. There are several reasons for this that are rooted in the preclinical, translational, and pivotal phases of studies, the intransigent biology of SCI, and even in the politics of clinical trials. The daily reality of SCI occurrence and its permanent outcomes drives the machinery of clinical translation. Other factors that impact progress and decision-making in the neuroprotective therapeutics field include the organization of medical care competition, market forces, availability of research funding, the media and public perception, high-status publications, and the energy and leadership of investigators. Clinical factors that complicate therapeutics trials include human variability, the unique context of each injury, variations in management, secondary complications, and type and extent of rehabilitation. Clinical trial methodology to address subject and injury heterogeneity may rely on stratification and partitioning methods [85, 322] as well as responder analyses [294]. Pharmacokinetic studies have rarely been performed in SCI neuroprotection trials, and recent evidence indicates that the systemic exposure to an enterally delivered neuroprotectant is highly variable between subjects [58]. This indicates that serum levels might be needed to guide the dosing schedule in order to *achieve uniform exposure to the drug* between individuals in a clinical trial. Dosage adjustment may also be required to achieve patient drug levels similar to those employed in key preclinical studies [49]. Unlike diseases such as liver and cardiac injury, there are no validated quantitative biomarkers available to provide insight into the real-time effects of CNS neuroprotectants [189] although serum light chain neurofilament has recently been reported to correlate with injury severity [151] and to be modified by minocycline treatment after cervical SCI [183]. Post-injury imaging is also rather insensitive to subtle neuroprotective effects although the relative rate and extent of T2 signal distribution is under investigation as a marker of injury severity [198]. Thus, clinical examination is the primary tool to assess efficacy. This is sensible when an intervention is potent but risks missing subtle signals that might be important guideposts to address issues of the therapeutic window, dose, pharmacokinetics, and duration of therapy.

It is considered that there are faults in the preclinical evaluation process [71, 123, 196]. A therapeutic should show a very reproducible and robust effect to have a chance to have an effect in a group of humans with SCI. Preclinical testing is performed in genetically similar animals using protocols that emphasize exact repetition. The intent is to minimize heterogeneity to achieve clarity. Confidence in the value of animal testing for SCI rests largely on success in other disease states such as cancer, diabetes, and organ transplantation. Highly reproducible SCI methods [347] and assessment techniques have been developed [19]. Despite these tools, it is frustratingly difficult for others to reproduce positive findings reported by another research group [304, 305]. The field is struggling with this issue especially after a

series of failed replications sponsored by NINDS. There is no easy solution to the replication problem, and apparently minor details can substantially affect experimental outcomes. There may be a role to consolidate testing into highly expert core facilities devoid of vested interest that can further perfect the art and science of replication beyond what has yet been achieved. Another important preclinical question is whether efficacy should be shown in more than one species before clinical translation [187] seems difficult unless an exact replication can be achieved in the rodent species. Often, the failure to replicate is left without a resolution that is unsatisfactory for the advance of our field.

Outcome measures in preclinical experiments should have a correlate to human recovery. For therapeutics to be used to recover function after cervical SCI, recovery of arm and hand function are critical issues. This raises a challenging question in the use of large animal models in so far as prominent models such as pigs are not useful for detailed assessment of hand function. The authors' opinion is that primate model testing is justified for high-risk therapeutics such as directly implanted cells but not for low-risk pharmacological interventions. Upper extremity assessments are available for rodent models of cervical SCI [8].

Typically, only positive reports are published. It would be valuable to the field to communicate the absence of therapeutic effects and the presence of adverse events and analyze the potential causes of failure (underpowered sample, unspecific outcome measures, underdosing, overdosing, incorrect therapeutic window, improper route of administration, etc.) and communicate these results. Another conclusion, given the complexity of secondary injury, is the expectation that a single agent will provide "remarkable" protection within the realities of a human clinical population is flawed. It may be essential to learn to combine multiple therapeutics that target several secondary injury mechanisms. As shown in this review, neuroprotectant testing has a long history in SCI. The field is continuing to mature and adding knowledge and technology at an impressive rate. The need for collaboration and standardization, data sharing, and data mining is increasingly evident and accepted. It would be beneficial if preclinical testing of future therapeutics could be extremely robust, independently replicated, tested in at least 2 species, and cleared of all reasonable concerns related to method of delivery before clinical testing is initiated. It is apparent that only full honesty and maximum diminution of bias will lead to efficient and meaningful progress in SCI neuroprotection. It may be that the field needs a fundamentally new approach as all of the foregoing suggestions are really methods to improve the current basic model. This model of preclinical prediction in animal models and then staged translation to humans appears to be inherently unreliable. Therefore, in conclusion there is an opportunity and need for insight and innovative approaches to advance this field.

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Neuroregeneration

21

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Abstract

The last three decades of research in spinal cord injury have led to a better understanding of mechanisms underlying the regenerative failure in the adult mammalian central nervous system (CNS). Together with an enormous progress in cell and molecular biology, it now seems for the first time possible to develop novel therapeutic approaches that address factors extrinsic and intrinsic to injured neurons and their axons to promote functional recovery after spinal cord injury. Neutralizing inhibitors of axonal growth, delivery of growth factors and cellular transplants, and modulation of the axonal cytoskeleton and genetic and epigenetic programs after CNS trauma hold promise as new therapeutic avenues. In this chapter, we will discuss the preclinical rationale of some promising neuroregenerative approaches that have the potential to be translated into clinical trials or are currently in initial phases of clinical testing.

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21.1 Introduction

Spinal cord injury (SCI) results in the loss of neural parenchyma, including neurons and glia, and the disruption of ascending, descending, and intraspinal projections (see chapter 19). The disruption of neuronal networks due to primary and secondary damage severely affects sensory, motor, and autonomic circuits. Neuroprotective approaches, (see chapter 20) provide a potential means during the early phase of injury to limit long-term functional deficits. In subacute to chronic phases of injury, function can only be restored if remaining connections compensate for the lost axonal connections or if axons regenerate or sprout to form new connections. Whether axonal growth after central nervous system (CNS) injury is considered regeneration or sprouting depends on whether a growing axon has previously been injured: axonal growth from an injured axon is considered regeneration, whereas growth from a non-injured projection is considered sprouting. Regeneration of an injured axon can occur from its cut end, from its shaft (formation of new branches), or by elongation of a preexisting non-injured branch. By contrast, sprouting of uninjured axons occurs as compensatory mechanism in response to injury of other axons (Fig. 21.1).

Axons in the peripheral nervous system (PNS) retain the ability to regenerate after injury throughout adulthood, whereas CNS axons do not. For a long time, the dogma

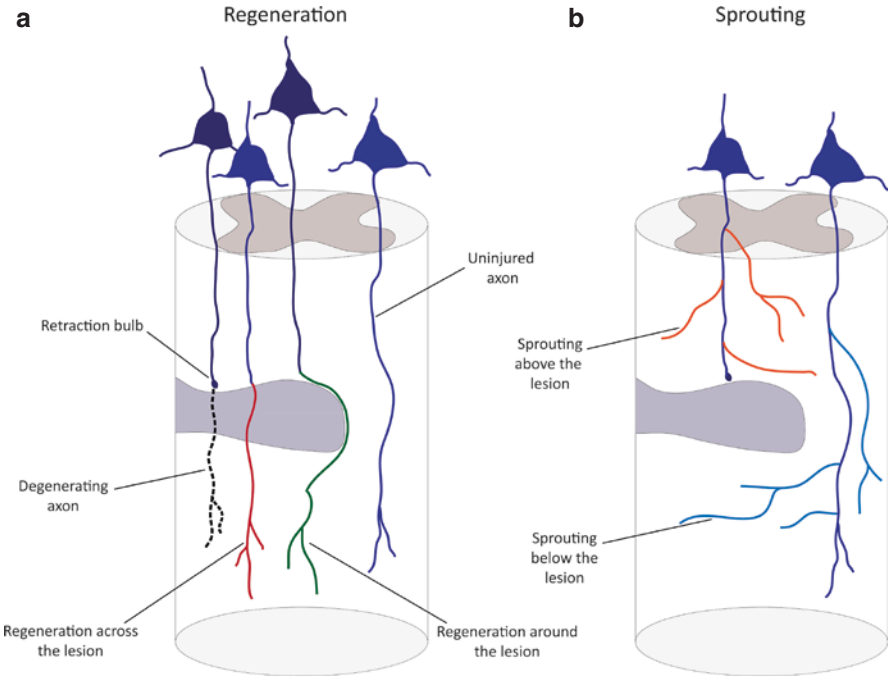

Fig. 21.1 Axonal degeneration, regeneration, and sprouting after spinal cord injury. (**a**) Injured non-regenerating axons display dystrophic retraction bulbs and Wallerian degeneration of the distal axon segment. Axon regeneration can occur into and across the lesion site or around the lesion. (**b**) Sprouting of injured and non-injured spared axons can be observed above or below the lesion site

that adult CNS neurons are unable to regenerate held true, as there was no evidence of CNS axon growth even into permissive peripheral nerve tissue implanted into the brain of rabbits [148]. However, subsequent studies demonstrated that the central branches of dorsal root ganglion (DRG) neurons are capable of intraspinal regenerative sprouting after partial denervation of the spinal cord in cats [157]. CNS regeneration remained controversial for several decades [115] until experiments by Aguayo and colleagues provided final proof that transected CNS axons can regrow into bridges of growth-permissive peripheral nerves implanted into the rodent spinal cord [1, 218]. This led to the hypothesis that CNS neurons are not generally incapable of regenerating but are rather hampered by the inhibitory nature of the CNS environment encouraging approaches to counteract this inhibition [41]. Subsequent studies have suggested that overcoming environmental cues alone is not sufficient to obtain robust CNS regeneration: CNS neurons display a lower growth potential than peripheral nervous system (PNS) neurons even on a permissive substrate in vitro, and this is associated with the limited activation of cell intrinsic programs after an axotomy [48].

Thus, current data suggest that the difference in the regenerative capacity of PNS and CNS is not only due to extrinsic factors acting primarily at the injured axon tip but also due to neuron-intrinsic differences. Extrinsic factors include the lack of positive growth signals present in PNS but not in the CNS, like laminin and Schwann cell-secreted factors, and the presence of negative cues accumulating at the site of injury in the CNS but not in the PNS including myelin-derived inhibitors, ephrins, semaphorins, and proteoglycans. Therefore, to address extrinsic influences, provision of a more permissive substrate, neutralization of the inhibitory CNS environment, and growth factor delivery have been investigated as a means to enhance CNS regeneration. More recent investigations have also focused on the intrinsic regenerative potential, which is regulated by a wide range of cellular processes including membrane and cytoskeletal reorganization, metabolic changes, axonal transport, local protein translation and signaling cascades, and the activation of a pro-regenerative genetic program.

21.2 Extrinsic Factors in Axonal Regeneration

21.2.1 Inhibitors of Axonal Regeneration and Sprouting

Axonal regeneration and neuroplasticity are limited by neurite growth-inhibitory molecules in the CNS, in particular after injury. The cellular and molecular responses that contribute to the inhibitory environment after CNS injury are now much better understood, and means to overcome growth inhibition have moved from in vitro neurite growth assays and preclinical animal models to clinical studies. Major components of the inhibitory environment after CNS injury include the fibroglial scar within and around the lesion, proteoglycans in the extracellular matrix, myelin-based inhibitors in particular in white matter, and several soluble repulsive factors.

21.2.1.1 The Fibroglial Scar

After SCI, a fibroglial scar consisting of different cells and extracellular matrix is formed within and around the lesion epicenter. Historically, the astrocytic scar was

thought to be the main impediment for axonal regeneration. Indeed, hypertrophic astrocytes dominate in the lesion penumbra, but the lesion core contains a heterogeneous mix of cells, including $NG2^+$ glia/oligodendrocyte precursor cells, meningeal and/or vascular fibroblasts, pericytes, ependymal cells, and phagocytic macrophages [245]. Disruption of the meninges is associated with infiltration of meningeal fibroblasts, which form a fibrotic scar and contribute to the inhibitory environment by promoting astrocytic reactivity [278] and by expressing repulsive guidance molecules [101]. However, the glial scar also stabilizes the injured parenchyma by reestablishing its physical and chemical integrity, closing the blood–brain barrier, reducing the infiltration of non-CNS cells, and limiting possible infections [35]. Ablating hypertrophic astrocytes or impeding their reorganization into a sealing cellular barrier is deleterious and results in invasion of inflammatory cells beyond the lesion, an increase in lesion volume, and functional deterioration [75, 117, 196, 279]. Thus, the classical view of the glial scar as deleterious in CNS injuries has clearly been refuted. However, at the same time the fibroglial scar constitutes a physical and molecular obstacle to regenerating axons. Several experimental strategies have attempted to modify the growth-inhibitory fibroglial scar. These include means to prevent the deposition of collagenous matrix [233], blocking TGF-ß [2, 58, 59], which contributes to astrocyte gliosis, making astroglia more permissive for growth by overexpressing cell surface molecules such as L1 or PSA-N-CAM [45, 71, 228, 290] or cell transplantation (discussed below). Besides the physical and cellular barrier generated by the fibroglial scar, factors produced in and around the lesion site actively prevent axonal growth into and beyond a lesion in the injured spinal cord. The most important inhibitory factors are discussed below.

21.2.1.2 Proteoglycans

One class of molecules present in the extracellular matrix of the glial scar actively inhibiting axon outgrowth are chondroitin sulfate proteoglycans (CSPGs). CSPGs consisting of a protein core and glycan side chains are strongly upregulated at sites of CNS injury [132, 133, 175]. In the 1990s, in vitro studies established a clear link between astrocytes, CSPG secretion and inhibition of neurite outgrowth. Astrocyte lines producing a nonpermissive matrix were poor promoters or inhibitors of axon growth, which was reversed by treatment with inhibitors of proteoglycan synthesis [248–250]. In vivo studies demonstrated that upregulation and distribution of CSPGs in the scar tissue after SCI contribute to the failure of axon regeneration [61, 62]. CSPGs are also present throughout the CNS around cell soma and dendrites in perineuronal nets and thereby limit plasticity in areas of the CNS not directly affected by injury [171, 245]. Digestion of glycosaminoglycan (GAG) side chains of CSPGs with the bacterial enzyme chondroitinase ABC (ChABC) can attenuate its inhibitory activity, and the first evidence that the enzyme is effective in vivo in animals with spinal cord contusion injuries suggested that CSPG digestion could be of therapeutic value [153]. Indeed, intrathecal delivery of ChABC after cervical dorsal column lesions was shown to promote regeneration of ascending sensory and descending corticospinal projections in rodents, electrophysiological improvements, and partial recovery of sensorimotor function [30]. Subsequent studies have confirmed the beneficial effects of ChABC treatment after SCI, including enhanced

regeneration of lesioned axons [37, 38, 244, 289], enhanced sprouting and connectivity of spared pathways [11, 30, 171, 253], immunomodulatory mechanisms [66], and neuroprotection [42, 43].

Both somatic and autonomic motor recovery was observed after digestion of CSPGs [30, 38, 152]. Most studies conducted to date were done in rodent models of SCI, with few studies in larger animals such as cats [261] and squirrel monkeys [27]. However, studies in larger animals are likely needed to assess the safety and efficacy of ChABC treatment and to better estimate required dosage and develop suitable means of delivery. Studies with ChABC in dogs are currently ongoing (http://vetmed.iastate.edu/vmc/small-animal/clinical-trials/chondroitinase-clinical-trial-0). In recent years, combined delivery of ChABC with other approaches, such as immunomodulation [110], cell and peripheral nerve transplantation [4, 44, 86, 152, 267], delivery of neurotrophic factors [95, 124, 137], antibodies against myelin-based inhibitors (anti-Nogo-A) [291], or rehabilitation [276], has shown that such combinatory treatments are even more effective.

Although beneficial effects of ChABC have been observed and validated across several independent laboratories in different animal models, clinical translation remains challenging. ChABC rapidly loses its enzymatic activity at body temperature, and therefore repeated injections are needed, with increased risk of infections due to the invasive route of application. This issue has been partially addressed by thermostabilization of the enzyme, delivery within hydrogel scaffolds, generation of ChABC-secreting cell lines, and delivery by viral vectors [13, 125, 137, 223]. However, long-term delivery by viral gene transfer might pose additional problems, as the consequences of prolonged or permanent CSPG degradation are unknown.

Recently, receptors mediating the inhibitory activity of CSPGs have been identified and include the protein tyrosine phosphatase σ (PTPσ), the phosphatase leukocyte common antigen related (LAR), and the Nogo receptors 1 and 3 (NgR) [65, 81, 242]. The overlap in receptors for Nogo (see below) and CSPGs [65] indicates that shared mechanisms for neurite growth inhibition by myelin-associated inhibitors and CSPGs exist. Peptides blocking LAR or PTPσ receptors preventing CSPG binding increase serotonergic axon sprouting after SCI in mice, and LAR knockout mice show better functional recovery after SCI [81, 147]. Intracellularly, CSPGs inhibit neurite growth by signaling through the Rho GTPase/ROCK pathway [64, 177, 186], and inactivation of Rho by C3 transferase is one means to modulate responses to growth-inhibitory CSPGs [64]. A formulation of C3 transferase (Cethrin) that is cell permeable and blocks Rho activation [161] has moved to clinical trials [77]. The phase I/IIa study with a small number of patients does not allow conclusions about treatment effects, but a trend toward larger motor recovery was evident [176]. Ibuprofen has also been suggested as a potential candidate to modulate Rho activity, and several reports have indicated an effect of high doses of ibuprofen in animal models of SCI [143].

21.2.1.3 Other Inhibitory Molecules

In addition to CSPGs, several other classes of potent growth-inhibitory molecules are upregulated after SCI and are expressed by cells within and around the lesion site including semaphorins, ephrins, and Eph receptor tyrosine kinase family members, Wnts and netrins [101, 103, 193, 198].

Members of the Eph protein family are upregulated for several weeks post-injury in the rodent spinal cord [52, 127]. EphA and EphB3 receptor expression is increased in glia and neurons [185, 284]; ephrinB2 can be detected on reactive CNS astrocytes, and its receptor EphB2 is present on infiltrating fibroblasts, suggesting a close interaction between the different cell types [33, 74]. EphrinB3 expressed by adult oligodendrocytes has also been identified as a strong inhibitor of axon regeneration [16]. Soluble inhibitors of Eph4A signaling (ephrin-5A-Fc or Eph4A-Fc) or EphA4-blocking peptides have shown to promote some improvement in axon growth [74, 104].

Meningeal fibroblasts, contributing to the lesion scar, are known to express semaphorins [201], and pharmacological inhibition of Sema3A resulted in improved regeneration and/or preservation of injured axons, Schwann cell-mediated myelination, a decrease in apoptosis, and better functional recovery after SCI in rats [136]. Taken together, these findings indicate that blocking of semaphorins or of Eph/ephrin signaling could represent a viable option to promote regeneration after SCI.

Less is known about Wnt signaling, but canonical Wnt signaling seems to be involved in astrogliosis and repulsion of at least some axonal populations [119, 121, 221].

21.2.1.4 Myelin-Associated Inhibitors

The concept that adult CNS myelin contains growth-inhibitory components was proposed more than 30 years ago. This was based on the fact that CNS axons can regenerate in peripheral nerve transplants [57, 218], while PNS axons extend only poorly on CNS tissue [235]. In fact, even PNS neurons display more limited neurite extension on CNS myelin than on PNS myelin [76, 236].

The proteins underlying the contact-mediated inhibition of neurite growth were isolated, and an antibody (IN-1) against the inhibitory myelin component was shown to partially neutralize its growth-inhibitory effect [41]. Based on this information, the gene was identified and cloned and is now known as Nogo-A [46, 107, 207]. In parallel, other myelin-associated components have been identified that have potent inhibitory activity on neurite outgrowth [97]. These include myelin-associated glycoprotein (MAG), oligodendrocyte myelin glycoprotein (OMgp), and CNS myelin lipid sulfatide [156, 178, 277, 285]. All myelin inhibitors signal via a common receptor (NgR) in a complex with Lingo-1 and TROY or p75. Activation of NgR induces axonal cytoskeletal rearrangements and retrograde transport to the cell body, where it exerts further inhibitory functions via a signaling pathway involving the small Rho GTPase, RhoA, and Rho-associated kinase (ROCK) [68, 199].

Although MAG and OMgp represent a nonpermissive growth substrate, experimental ablation of MAG did not abolish the inhibitory effect of CNS myelin in vitro and in vivo [12]. Equally, ablation of Nogo-A or its receptor in mice resulted in contradictory findings promoting regeneration or having no effect on axon growth [36, 67, 140, 150, 151, 246, 292, 293]. One potential explanation for the limited effects in knockout animals is the presence of multiple other inhibitors; thus deletion or neutralization of a single inhibitory component or receptor complex can only have limited effects. As MAG, OMgp, and Nogo-A seem to signal through the same

Nogo receptors (NgR), and overlap in inhibitory signaling from CSPGs exists, intracellular signals downstream from the receptor might have a higher likelihood of being therapeutically active.

In one of the first studies demonstrating an effect of antibodies against Nogo-A, intrathecal infusions of the monoclonal antibody IN-1 raised against two inhibitory antigens (NI-35 and NI-250, now known as Nogo-A) [41] enhanced sprouting of injured corticospinal axons in rats [234]. Several studies confirmed some of these findings across different animal species, including nonhuman primates. Nogo-A was targeted in vivo by different anti-Nogo antibodies, the NgR-blocking peptide NEP1-40 or a soluble Nogo receptor fusion protein (NgR-Fc) [84, 87, 90–92, 106, 140, 155, 189, 255]. In rodents, treatment with anti-Nogo-A led to enhanced regenerative sprouting, midline crossing of unlesioned contralateral CST fibers after unilateral pyramidotomy, some regeneration and faster recovery of sensory function, and locomotion [155, 210, 263]. Similarly, anti-Nogo-A-treated nonhuman primates subjected to unilateral spinal cord transection at the cervical or thoracic level showed corticospinal axon sprouting and recovery of manual dexterity of the ipsilesional hand, although this recovery was discussed controversially [84, 92, 270].

Based on the preclinical evidence, a humanized, recombinant anti-Nogo-A antibody was produced by Novartis for clinical application. Toxicological studies were performed in rodents and primates. Phase I of the anti-Nogo-A clinical trial, sponsored by Novartis, was started in 2006 within the EMSCI network of spinal cord centers (European Multicenter Study about Spinal Cord Injury, EMSCI; http://clinicaltrials.gov/ct2/show/NCT00406016). Furthermore, anti-Nogo-A (ozanezumab) was tested in ALS patients, as Nogo-A has been proposed as an early diagnostic biomarker of ALS (http://clinicaltrials.gov/ct2/show/NCT00875446). Ozanezumab was well tolerated and only six adverse events were reported, none of which was related to the drug. Immunohistochemical analyses of frozen sections of muscle biopsies from ALS patients showed co-localization of ozanezumab and Nogo-A [181]. Results from the trial in SCI patients have not been published to date. Although both clinical trials were successfully completed, a phase II trial is only now being initiated in Europe.

21.2.2 Neurotrophic Factors

Besides the inhibitory environment in the injured spinal cord, the absence of permissive growth substrates at the lesion, insufficient stimulation of axon growth, and a lack of guidance (chemotropic or physical) for regenerating axons contribute to the regenerative failure. During development and after injury in the PNS, neurotrophic factors play an important role in neuronal survival, axonal growth, and target innervation. Several families of trophic factors including members of the neurotrophin family (nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), neurotrophin-4/5 (NT-4/5)), GDNF family ligands (glial cell line-derived neurotrophic factor (GDNF), neurturin (NRTN), artemin, persephin), neuropoietic cytokines (ciliary neurotrophic factor (CNTF), leukemia

inhibitory factor (LIF)), and others have therefore been investigated for their influence on neuronal survival and axon growth after SCI. In addition to infusions and injections of protein, numerous studies employed cells genetically modified to express neurotrophic factors or direct in vivo viral gene delivery to enhance survival, sprouting, and regeneration.

21.2.2.1 Effects on Neuronal Survival and Atrophy After SCI

Neuronal atrophy and cell death can be consequences of axotomy depending on the distance to the cell soma and the affected neuronal population. After SCI, most spinal projection neurons in the brain do not die but some become atrophic. In fact, the survival of injured neurons is reflected in the presence of dystrophic end bulbs of axotomized neurons, which can be found at and around the lesion site in SCI patients even over 40 years after the trauma [227]. The shrinkage of cell bodies has sometimes been mistaken for cell death, but more accurate methods for cell counts have in most cases not confirmed neuronal loss.

One of the clearest examples for SCI-induced neuronal atrophy can be observed in the red nucleus. Rubrospinal neurons shrink after cervical spinal cord lesions and BDNF delivery in the vicinity of the cell soma, either acutely or even 18 months post-injury, can prevent or reverse neuronal shrinkage [142, 144, 226]. Corticospinal neuron cell death after subcortical lesions or atrophy of CST neurons after SCI can also be amended by BDNF [31, 100, 162]. Another example is the effect of NT-3 in rescuing spinal projection neurons [29] and neurons in Clarke's nucleus in the spinal cord [243].

21.2.2.2 Neurotrophic Factors in Regeneration and Sprouting

In addition to promoting neuronal survival, neurotrophic factors also promote axon growth during development, after PNS injuries and following neurotrophic factor delivery to the injured spinal cord. Many animal studies examining axonal responses to growth factor delivery have used grafts of cells genetically modified to overexpress neurotrophic factors. Depending on the trophic factor expressed, projections from the brain stem such as rubrospinal, raphespinal, cerulospinal, reticulospinal, and spinal projections including propriospinal, spinal motor axons, and primary sensory axons have been shown to extend into growth factor-producing cellular grafts such as fibroblasts [20, 22, 108, 109, 118, 129, 130, 179, 190, 271], Schwann cells [182, 280], bone marrow stromal cells [164, 165], olfactory ensheathing cells [39, 224, 225], neural precursor cells [40, 160], or peripheral nerve grafts [24].

Most axonal populations responding to different trophic factors (Table 21.1) densely penetrate growth factor-producing grafts except for corticospinal axons, which have only convincingly been shown to penetrate grafts of fetal spinal cord. While NT-3 delivery promotes corticospinal sprouting, growth is only observed in the host parenchyma surrounding the lesion or in the distal spinal cord if some spared projections remain [24, 47, 83, 108, 224, 294].

Despite the robust axonal growth of some axonal populations into a lesion site filled with neurotrophic factor-releasing cells, axons rarely exit the graft to extend into the distal host tissue. Thus, sustained cellular delivery of neurotrophic factors stimulates axon growth, but the inhospitable environment and the lack of a growth stimulus

Table 21.1 Axonal populations responding to cellular or viral neurotrophic factor delivery

Neurotrophic factor	Responding axonal populations	References
NGF	Nociceptive sensory	[109, 271, 280]
BDNF	Rubrospinal	[130, 145, 159, 225, 266]
	Reticulospinal	[130, 167]
	Raphespinal	[129, 164, 182, 266]
	Vestibulospinal	[130]
	Dorsal column sensory	[164]
NT-3	Dorsal column sensory	[5, 122, 260]
	Corticospinal	[47, 83, 108, 224, 294]
NT-4/5	Propriospinal	[22]
	Raphaespinal	[22]
GDNF	Dorsal column sensory	[20]
	Nociceptive sensory	[20]
	Propriospinal	[20, 63]
IGF-1	Raphaespinal	[120]

beyond the lesion site remain an obstacle for long-distance axonal bridging across the lesion site. Even if transient, regulated cellular delivery of the neurotrophin BDNF is used, axons do not extend beyond the graft, although transient growth factor delivery is sufficient to sustain regenerated axons in the lesion [21]. Only in the presence of a growth stimulus distal to the cell graft, axons can exit the lesion. Using virus-based in vivo gene delivery (lentivirus or adeno associated virus (AAV)), gradients of NT-3, BDNF, or GDNF within the distal host tissue can be generated, allowing for bridging axonal regeneration of dorsal column sensory axons, reticulospinal axons, and propriospinal axons, respectively [5, 63, 134, 166, 167, 260]. Successive regulated gradients of neurotrophic factors might further increase the distance covered by regenerating axons.

In addition to regeneration of injured axons, neurotrophic factors can also promote sprouting and structural rearrangement of spared connections, as well as changes at the cellular and synaptic level (reviewed in [28, 173, 282]. Collateral sprouting is functionally highly relevant and contributes to spontaneous neurological recovery in animal models of SCI and most likely in patients with incomplete SCI. Such naturally occurring neural rearrangements that have been extensively investigated in rodents represent an attractive target to enhance functional recovery [7, 10, 53, 281]. Collateral sprouting of spared projections after neurotrophic factor delivery has been shown for corticospinal axons in response to NT-3 delivery [47, 294] and for reticulospinal projections and serotonergic axons [231] after BDNF delivery to name a few.

21.2.2.3 Adverse Effects and Difficulties in Clinical Translation

While there is strong evidence for the pro-regenerative activity of growth factors in the injured spinal cord, potential adverse effects pose challenges for the translation of findings from animal models. This is partially due to the widespread distribution of receptors but also depends on the duration and the amount of growth factor delivery. Intraventricular and intrathecal infusion via osmotic mini-pumps lead to

widespread distribution of growth factors, and long-term delivery can result in Schwann cell proliferation, weight loss, and nociceptive fiber sprouting as demonstrated for NGF infusions. Intraparenchymal in vivo gene delivery or grafting of genetically modified cells can partially overcome these issues. However, a reliable means to turn off neurotrophic factor expression in virus-transduced cells is needed as long-term growth factor expression results in graft expansion likely by Schwann cell proliferation [20, 22]. In addition, sustained high levels of growth factors within a lesion site will not promote axon extension across a lesion site. Only few studies have examined regulatable neurotrophic factor expression indicating that regenerated axons are at least partially sustained once growth factor expression is turned off [21, 122]. High doses of BDNF delivered by viral vectors are needed for axons to regenerate across a lesion site but can also induce spasticity-like symptoms and hyperreflexia in rats after cervical or sacral SCI [85, 167]. Taken together, only a very localized, transient, and possibly cell-restricted elevation of growth factors might be suitable for clinical translation.

21.3 Neuron-Intrinsic Factors Influencing the Regenerative Capacity

The growth capacity of CNS axons declines during development as connections mature and synapses are formed (see chapter 2). This decline is accompanied by the downregulation of growth-associated genes and is also ultimately reflected in the regenerative failure of adult CNS neurons. However, based on the responses of different axonal populations to a variety of growth-promoting stimuli, differences in the regenerative capacity seem to exist in the adult spinal cord. Sensory axons seem to have the highest competence for regeneration followed by propriospinal and brain stem projections. Corticospinal neurons are most refractory to regenerative approaches. The ability of peripheral sensory neurons to mount a regenerative program after PNS injury has been a major focus in identifying genes and signaling cascades important for axon regeneration. Indeed, if injury to the central projections of dorsal root ganglion neurons in the spinal cord is preceded by a lesion in the PNS, regeneration can even be observed in the spinal cord. This so-called conditioning effect is based on the activation of regeneration-associated genes in DRG neurons and has served as a model to identify mechanisms underlying intrinsically regulated regenerative programs [191, 217]. Transcriptional and epigenetic mechanisms, local protein translation, retrograde and anterograde axonal transport, and cytoskeletal dynamics have been identified as intrinsic key regulators of axon regeneration.

21.3.1 Calcium Transients and Elevation of cAMP

When axons are injured, calcium influx into the axoplasm is one of the first consequences (see chapter 19). This transient intracellular calcium wave propagating from the injured axon to the cell soma seems to be crucial for resealing the axonal

membrane, protein synthesis, cytoskeleton rearrangement, assembly of the growth cone, and the activation of intracellular signaling cascades. Axotomy-induced calcium influx leads to increased cAMP levels in neurons capable of initiating a regenerative response. Increases in cAMP levels are necessary for growth cone assembly [99] and can partially overcome myelin-associated repulsive signals in vitro and in vivo [184, 251, 252]. Injection of a cell permeable cAMP analogue (dibutyryl-cAMP; db-cAMP) into DRGs partially mimics a conditioning lesion enhancing the regeneration of injured dorsal column axons [166, 192, 208]. An alternative approach to increase cAMP levels is the administration of phosphodiesterase (PDE) inhibitors to limit the degradation of cAMP. Delivery of the PDE4 inhibitor rolipram led to enhanced regeneration, attenuation of the glial scar, and some functional recovery in rodents [194]. The pro-regenerative and neuroprotective effects of rolipram, as well as the functional improvement were also reported in contusive animal models of SCI [14, 51, 126]. However, systemic PDE inhibitors act on numerous other neuronal populations with adverse effects such as severe nausea, and changes in the expression of growth-associated genes are very transient by increasing cAMP [23]. Clearly, increases in cAMP are not solely responsible for the molecular cascades orchestrating a regenerative response.

21.3.2 Epigenetic Regulation of Regeneration-Associated Genes (RAGs) and Growth Cone Dynamics

When the calcium wave reaches the soma of DRG neurons, it leads to activation of PKCμ and export of histone deacetylase 5 (HDAC5) from the nucleus. As a consequence, increased histone acetylation contributes to the pro-regenerative transcriptional program, and local tubulin deacetylation at the axon tip by HDAC5 and HDAC6 results in increased microtubule dynamics and axon regeneration [49, 50]. HDAC5 nuclear export is followed by increased acetylation of histone 4 (H4) in the promoters of regeneration-associated genes (RAGs), which leads to their induction. Several transcription factors including Jun, KLF4, KLF5, Fos, ATF3, and Gadd45g, as well as Smad1, Sprr1, Galanin, NPY, and VIP, which have been associated with the injury-induced response and axon growth, have been found to be HDAC5 regulated [50, 80]. Independently, the histone acetyltransferase CBP/p300 regulates RAG expression via histone 3 (H3) acetylation of p53, GAP-43, and Sprr1 [96]. Thus, epigenetic mechanisms might play a key role in axon regeneration.

21.3.3 Manipulation of the Cytoskeleton

Injured PNS axons maintain stable proximal microtubuli and have dynamic microtubuli at the tip of their growth cone, whereas injured CNS axons form retraction bulbs with a disorganized network of microtubuli, a rather static structure that can persist for years after SCI [227]. After nuclear export, HDAC5-mediated deacetylation of microtubuli at the axon tip of DRG neurons increases their dynamics and

reorganization. This is a prerequisite for the formation and motility of growth cones, which are necessary for growth initiation and axonal extension [49, 50]. On the other hand, selective inhibition of HDAC6 and the consequent increase in acetylated, stable microtubuli enhance survival after oxidative stress and growth of CNS neurons on nonpermissive substrate [220]. Thus, microtubule stability might have divergent effects on axon regeneration. Nevertheless, pharmacological stabilization of microtubuli can promote growth cone formation and dynamics. Moderate stabilization of microtubuli by low doses of Taxol, a cancer drug that inhibits cell division by interfering with the microtubule network, has been shown to prevent the formation of retraction bulbs, decrease axonal degeneration in vivo, and enable CNS neurons to overcome the growth-inhibitory effect of myelin in vitro [73]. In the injured rat spinal cord, intraparenchymal Taxol delivery led to a reduction of the fibrotic scar in a TGF-ß-dependent manner, decreased levels of inhibitory CSPGs at the lesion, and increased the density of serotonergic fibers distal to the lesion. Moderate functional recovery was observed in Taxol-treated animals after mild contusion injuries [116]. These data were partially reproduced in a recent replication study showing changes in the extracellular matrix composition at the lesion but no functional improvements [206]. Experiments in the optic nerve also support the conclusion that Taxol can enhance regeneration and limit scar formation after injury [239]. Using a Taxol derivative, EpothiloneB, which can cross the blood–brain barrier, further supported functional recovery with this approach [227]. Taken together, despite some convincing preclinical evidence, additional studies are needed to define the dose, time window of treatment, and maximum benefit before moving toward clinical translation.

In addition to microtubuli, actin cytoskeleton dynamics play an essential role in growth cone extension. As mentioned in the description about inhibitory molecules in axon regeneration, myelin-based inhibitors and proteoglycans exert their inhibitory effect by activation of the small GTPase Rho, which acts as an intracellular molecular switch. RhoA and related GTPases act via several intermediaries on the actin cytoskeleton leading to depolymerization of actin filaments and growth cone collapse. Thus extrinsic and intrinsic regulators of regeneration closely interact and cannot always be clearly separated.

21.3.4 Transcriptional Networks and Other Signaling Cascades

The orchestrated response of DRG neurons after PNS injury leading to the upregulation of regeneration-associated genes is not only controlled by the initial calcium wave propagating from the site of injury to the cell soma but also by the retrograde transport of locally activated injury signals containing a nuclear localization sequence [15, 183]. Among the identified candidates are activated kinases (ERK, JNK) and transcription factors like STAT3. Several gene array studies have characterized the time course and extent of gene expression changes during PNS regeneration identifying an ever-increasing set of RAGs. Because CNS neurons fail to effectively activate many of these RAGs [78], means to promote CNS axon growth

by gene delivery of RAGs or by manipulating pathways that lead to the upregulation of RAGs have been explored in numerous studies. Among the first genes investigated in these studies was GAP43 [3]. In addition, transcription factors that might have more broad effects by influencing numerous other genes have been explored in this context including SMAD1 [296], CREB [94], STAT3/SOCS3 [247], ATF3 [237], c-JUN [211], and others. Among these, STAT3 and c-JUN are perhaps those with the strongest indication for a pro-regenerative effect; however none of these experiments promoted regeneration to the same degree as conditioning lesions. In vitro high-throughput screens for transcription factors that enhance or inhibit axon growth have also identified members of the Kruppel-like factor (KLF) family as potential transcriptional repressors or enhancers of axon regeneration, and KLF7 can also promote corticospinal axon regeneration and sprouting in vivo after overexpression [18, 187].

Besides transcriptional networks, regulators of translation have also been shown to be involved in the regenerative program. The activity of mTOR, a regulator of protein translation, is strongly influenced by PTEN. Elimination of the tumor suppressor gene PTEN induces robust axon growth of retinal ganglion neurons [200]. Further investigations demonstrated that mTOR activity also regulates sprouting responses of CST neurons after injury. Conditional deletion of PTEN attenuated injury-induced loss of mTOR activity in CST neurons and enhanced sprouting and regenerative growth indicating that this signaling pathway represents a promising approach to target the intrinsic regenerative capacity of neurons after SCI [56, 98, 158]. Combining PTEN deletion with the activation of the STAT3 pathway showed even more remarkable growth after an optic nerve crush injury [247, 256].

21.3.5 Cell Transplantation

The therapeutic approaches reviewed above aim to enhance regenerative axon growth and/or sprouting of injured and spared projections by targeting either extrinsic or intrinsic factors. The regenerative capacity of endogenous projections remains, however, very limited, and axons only extend for modest distances. Considering the long distance that regenerating axons need to cover in the human spinal cord, robust long-distance target reinnervation after severe spinal trauma might be utopic. Moreover, boosting axon regeneration alone does not lead to restoration of neural tissue integrity and function. Neuroregenerative approaches might therefore be more effective in combination with cell replacement strategies, which promote anatomical and functional repair. Cell transplantation should ideally (1) provide a permissive physical and cellular substrate for axon growth, (2) promote axon regeneration, (3) allow for remyelination of regenerating axons, and (4) replace neurons and glia lost due to injury.

While a number of different cell types have been used in animal models and in initial clinical trials (Table 21.2), the “ideal” cell transplant covering all these functions has not been identified. Certain neural stem cells might be closest to meeting these requirements. Because cells are complex biological systems, numerous

Table 21.2 Clinical trials for neuroregeneration after SCI

Category	Substance/ treatment	Target	Company/ sponsor	ClinicalTrials. gov ID number
Stem cells	Embryonic stem cell-derived oligodendrocyte precursors	Remyelination	Geron Asterias Biotherapeutics	NCT01217008 NCT02302157
	Fetal brain-derived neural stem cells	Remyelination	StemCells Inc.	NCT01321333 NCT02163876
	Fetal spinal cord-derived neural stem cells	Remyelination? Relay formation?	Neuralstem Inc.	NCT01772810
Peripheral glia	Schwann cells	Axon growth, remyelination	University of Miami	NCT02354625 NCT02354625
	Olfactory ensheathing cells	Remyelination Axon growth	Various investigators	NCT01231893 others not listed
BMSCs		Axon regeneration?	Various investigators	Too many to list
Inhibitors of axon regeneration	Rho inhibitor (Cethrin, BA210)	Rho	Bioaxone Biosciences	NCT00500812
	Ibubrofen	Rho Neuroprotection Axon growth	University of Berlin	NCT02096913
	Anti-Nogo antibodies (ATI355)	Axon sprouting/ regeneration	Novartis	NCT00406016

variables influence outcomes of cell transplantation experiments such as age and gender of the donor, cell source, culturing conditions, as well as means, site, and amount of delivery. Thus, different studies using similar approaches do not always come to the same conclusion. Some of the most studied cell populations are described below.

21.3.5.1 Mesenchymal Cells

Mesenchymal stromal or stem cells (MSCs) have been extensively used for transplantation into the CNS. These self-renewing/multipotent stem cells, isolated from the bone marrow, can differentiate into osteoblasts, adipocytes, and chondroblasts, as well as putative neural cells and myoblasts in vitro [128]. MSCs represent a very attractive and promising cell source for tissue repair because they can be easily obtained from autologous bone marrow, cryopreserved and expanded in a relatively short period of time [238]. In addition, cells are well tolerated, and there are no reports of adverse reactions in both autologous and allogeneic transplantations. Initial reports that MSCs can differentiate into neural cells in vitro and in vivo turned out to be incorrect and were based on cell fusion or the transient expression of a few neural markers [163, 275].

MSCs have been reported to have anti-inflammatory, neuroprotective, and pro-regenerative effects by decreasing demyelination and scar formation, promoting regeneration and guiding axons, and altering the inflammatory reaction via neurotrophic paracrine activity (reviewed in [170, 197]. Improvements of locomotor, sensory, and autonomic function, as well as reduction of neuropathic pain, were observed in many but not all studies in different animal models [154, 262]. However, benefits in well-conducted preclinical studies were modest raising the question whether an invasive transplantation procedure with potential adverse effects is justified. Nevertheless, a number of ongoing and completed clinical trials have assessed safety and potential beneficial effects of BMSC transplantation after SCI. While most of these trials only enrolled a small number of patients, and are unable to draw conclusions about clinical efficacy, no major adverse effects were observed [82, 273].

21.3.5.2 Stimulated Macrophages

Despite the potential detrimental role of the immune system in CNS injury, inflammation can also play a beneficial role after SCI. Macrophages are crucial for clearing extracellular matrix and cellular debris and secrete growth factors, thereby facilitating remyelination and axon growth. In the late 1990s, transplantation of nonactivated blood-borne macrophages after transection of the spinal cord in rodents led to enhanced regeneration and recovery of motor function [216], as well as decreased expression of the axon growth-inhibitory myelin protein MAG, increased angiogenesis, and Schwann cell infiltration [89]. In a later study, a skin biopsy was adopted as the source to activate autologous macrophages that were administered 8–9 days after a rat spinal cord contusion. This resulted in less pronounced syringomyelia and improved motor function [25].

In subsequent clinical trials, autologous macrophages activated by incubation with autologous skin biopsies were injected into the spinal cord caudal to the lesion [131, 141, 146]. In both clinical trials, transplantation was performed in ASIA impairment scale (AIS) A patients within 14 days after injury. While the macrophage cell therapy was well tolerated, no significant difference in primary outcomes (conversion from AIS A to B or C) between treated and control group was detected.

21.3.5.3 Schwann Cells and Peripheral Nerves

Schwann cells play a central role in PNS regeneration, express neurotrophic factors, provide a favorable extracellular matrix, and guide axons across a lesion after PNS injury. Equally important, Schwann cells can myelinate PNS and CNS axons, they can be harvested from peripheral nerve biopsies and can be expanded in vitro.

In animal models of SCI, peripheral nerve grafts and Schwann cells have been used for over 30 years [57, 70, 218] and were investigated in a variety of animal studies, mostly in rodents. From a translational perspective, peripheral nerve grafts have several limitations compared to Schwann cell suspension grafts. These include the difficulty of creating a suitable interphase between the host spinal cord and peripheral nerve and the potentially invasive nature of nerve grafting particularly after incomplete SCI. In contrast, in vitro cultivation of Schwann cells allows for the detailed characterization of cell properties and for the generation of a sufficiently

large number of cells that can be injected and distributed with limited manipulations in the parenchyma surrounding the lesion site via cell migration. For autologous transplantation, Schwann cells are usually harvested from the sural nerve resulting in limited functional impairment.

In rodent studies, Schwann cells have been transplanted in contusion/compression, hemisection, and full transection models of SCI [34]. Although several studies demonstrated that Schwann cells promote axon regeneration, only a limited number of axons can bridge the lesion site, and regenerated axons are not able to exit the graft to extend into the host tissue [286, 288]. When administered in combinatorial approaches with neurotrophic factors, degradation of inhibitory CSPGs or increases in cAMP, more robust regeneration is usually observed [8, 44, 63, 86, 102, 137, 182, 202, 280, 287]. In thoracic and cervical contusion models, slight improvements in motor function were also demonstrated after adult rodent Schwann cell transplantation [9, 232, 259].

Only few preclinical studies with human cells have been performed. Small behavioral benefits were observed, and about 1 % of axons were estimated to bridge across the lesion for a few mm. In contrast to other axons, corticospinal axons only entered grafts for very short distances and only when combined with FGF-1 [113, 114]. Based on the preclinical evidence, three clinical studies with Schwann cell transplants in SCI patients have been conducted to date. From the first two completed studies, only limited conclusions about efficacy can be drawn, but the transplantation procedure appeared to be safe [229, 230, 295]. Supported by safety and toxicity studies in rodents, minipigs, and primates, more recently, an FDA-approved phase I study transplanting autologous Schwann cells in patients with subacute neurologically complete, thoracic SCI was initiated, which is still ongoing [112] (https://clinicaltrials.gov/ct2/show/NCT01739023).

Future clinical applications will have to cope with some challenges:

1. Autologous isolation of Schwann cells requires sacrificing a peripheral nerve, and thus an alternative source would be desirable.
2. Expansion of nerve-derived Schwann cells or induction of Schwann cell differentiation from other cell sources [17] takes weeks to months.
3. In isolation without any additional interventions, Schwann cells seem to have only limited functional effects.
4. Cell survival following transplantation is rather low similar to other transplanted cells.

Nevertheless, Schwann cells remain a reasonable treatment approach for SCI. While current clinical studies might not show meaningful clinical benefit, the results could provide the basis for future studies combining Schwann cell transplants with other treatments that have shown promise in animal models.

21.3.5.4 Olfactory Ensheathing Cells (OECs)

Olfactory ensheathing cells (OECs) were first described in the nineteenth century by Golgi [105] and Blanes [19] as specialized glial cells exclusively located in the olfactory nerve and glomerular layers, one region of the CNS where axonal

regeneration is possible throughout adulthood. OECs ensheath and isolate olfactory axons from the growth-inhibitory CNS environment, enabling axonal transition from PNS to CNS, i.e., from the olfactory epithelium toward targets in the olfactory bulbs [69]. The unique axonal growth-promoting properties of OECs were confirmed in vitro and in vivo after dorsal root transections [212] as well as after complete thoracic transections [214]. In the following years, the pro-regenerative and neuroprotective effects of OECs were investigated in various rodent models of SCI in several dozen preclinical studies (reviewed in [213, 222]. These studies demonstrated that OECs do not only promote axonal regeneration in the injured CNS but also functional reconnection of injured axons, remyelination, formation of blood vessels, and reorganization of the glial scar and also display immunomodulatory properties [88, 222]. However, other studies showed only limited or no functional effects comparing OECs with Schwann cells [9, 203, 259]. This might be at least partially attributable to the source of the transplanted cells, culturing conditions, number of passages, and the site of injection [6, 213, 219].

The preclinical evidence encouraged the initiation of several clinical studies. In Australia OECs isolated from nasal biopsies were transplanted in patients with chronic SCI. These studies confirmed the feasibility and safety of the approach. While functional improvements were not detected, the studies with three to six patients were too small to draw definitive conclusions [79, 169]. Two subsequent clinical trials reported functional improvements [215, 257], but again, a limited number of patients were included. Larger clinical trials are needed to confirm the safety and efficacy of OECs for the treatment of SCI.

21.3.5.5 Neural Stem Cells: Remyelination and Relays

The cells described above have demonstrated some beneficial effects after SCI by increasing neuroprotection, enhancing remyelination, or promoting regeneration. However, none of these cells are native to the CNS and can therefore only partially restore and not replace all functions normally performed by CNS neurons and glia. CNS neural stem cells that can generate appropriate neuronal and glial phenotypes might be the most efficient way for functional restoration and tissue replacement. CNS astrocytes and oligodendrocytes can provide physical, trophic, and metabolic support and remyelinate spared axons, while neurons might serve as a relay station between axotomized neurons and their targets thereby bridging the lesion site (Fig. 21.2). Neuronal relays that forward ascending and descending information across a lesion would make long-distance axon regeneration across a lesion site unnecessary. Due to their potential to differentiate into all three neural lineages (i.e., neurons, astrocytes, and oligodendrocytes), neural stem cells (NSCs) or neuronal- and glial-restricted precursors have gained substantial interest in recent years.

NSCs can be obtained from different sources including adult NSCs from the forebrain subependymal zone or from the spinal cord [283] and fetal NSCs from fetal brain or spinal cord [209, 272, 274], from embryonic or induced pluripotent stem cells (ESCs, iPSCs) [258, 265, 268], or from somatic cells via fate conversion [264]. However, in comparison to non-CNS cell types, NSCs are more difficult to obtain, and the generation and expansion of cells take several weeks to months.

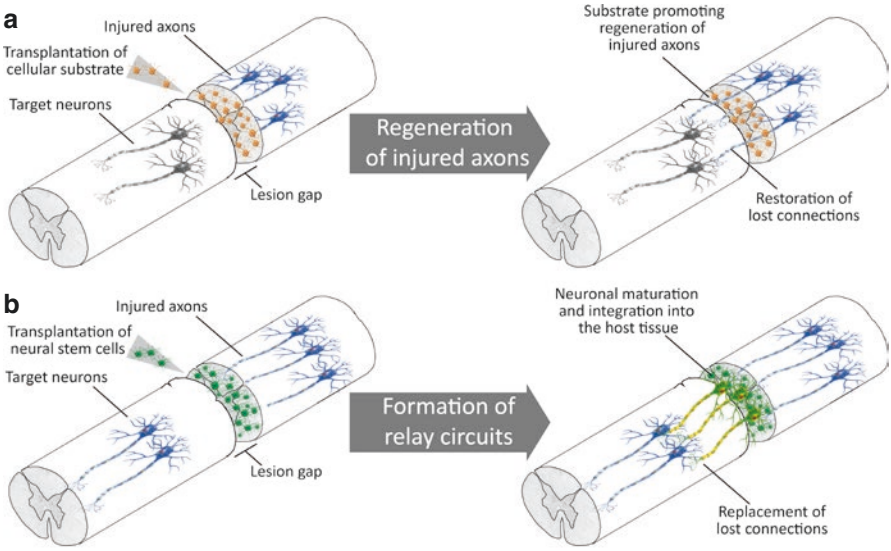

Fig. 21.2 Cell transplantation to promote axonal regeneration or neuronal relay formation. (**a**) Cellular transplants can provide a continuous substrate for axonal growth and promote regeneration of injured axons beyond the lesion site to restore connectivity. (**b**) Transplanted neural stem cells (*green*) or immature neurons that differentiate and mature can receive input from injured axons and reinnervate target neurons beyond a site of SCI. This new circuitry can serve as a cellular relay to restore the bidirectional communication between areas above and below the lesion

Human adult NSCs obtained during surgery or postmortem [188, 205] and fetal NSCs do not allow for autologous transplantation, and the use of fetal NSCs has some ethical implications. On the other hand, NSCs obtained from pluripotent stem cells or generated by fate conversion can be tumorigenic due to genetic or epigenetic changes [149]. Therefore, caution is advised although NSCs are therapeutically highly promising.

Numerous preclinical studies in SCI have examined the potential of NSCs to mediate functional recovery after SCI. In general, a portion of the transplanted NSCs survive, adopt mature neural phenotypes, and can integrate into the host tissue. However, the mechanisms leading to functional recovery are not always clearly defined. Transplanted cells can provide a substrate for regenerating axons [60, 180, 204], serve as a relay station [26, 123, 168], remyelinate spared projections [32, 54, 55, 111, 138, 174], or provide neuroprotection [72]. More recent studies have also reported that human-induced pluripotent stem cell-derived NSC can promote functional recovery [93, 168, 195, 269].

The first promising stem cell studies in SCI that led to clinical translation were based on the ability to generate large numbers of oligodendrocyte precursors from human embryonic stem cells to remyelinate spared axons and mediate functional recovery [139, 240]. Based on this evidence and additional studies, a phase I study

was initiated in 2009 by Geron Corp. to evaluate safety and efficacy of human ES cell transplantation in acute SCI [172]. After five patients underwent the cell transplantation procedure, the clinical trial was discontinued in 2011, apparently for financial reasons [135]. A different company (Asterias Biotherapeutics) has recently relaunched the program in subacute cervical SCI (https://clinicaltrials.gov/ct2/show/NCT02302157).

Two other cell lines that have led to clinical trials in SCI are based on fetal neural stem cells isolated from the brain and spinal cord, respectively. One phase I trial conducted in Canada and Switzerland sponsored by StemCells Inc. (https://clinicaltrials.gov/ct2/show/NCT01321333) in thoracic SCI at least 6 weeks post-injury has recently been completed, and a phase II study in cervical SCI has just started. This study with human fetal brain-derived NSCs is based on recovery mediated by remyelination after rodent SCI [54, 55, 272]. The second phase I study with thoracic AIS A patients sponsored by Neuralstem Inc. is still ongoing (https://clinicaltrials.gov/ct2/show/NCT01772810). The same cells were already used in a clinical trial with amyotrophic lateral sclerosis. Preclinical studies indicated that these cells extend axons in the injured rodent spinal cord for extended distances, form synaptic connections, and form a new relay circuit [168]. Similar results were also obtained with fresh fetal neural stem cells from rats [123, 168], but cells were found to migrate and form ectopic cell masses in CNS regions distant from the lesion site [254], and enhanced locomotor recovery was not observed in a reassessment study [241]. Such potential adverse effects might be due to the means of cell delivery via pressure injection and the lack of functional recovery in a replication study due to poor engraftment.

Conclusions

Progress over the last 30 years has provided important insights into the mechanisms underlying the limited regeneration of the adult nervous system. This has led to a continuously increasing number of clinical trials using pharmacological and cellular approaches. While a major breakthrough in regenerative therapies for spinal cord injury has not yet arrived, several novel concepts and important pathways have been identified and are currently tested in clinical trials. Possibly, single treatments will only be effective in partial injuries and not be able to restore substantial function after severe SCI given the complex interplay between neuron-intrinsic and extrinsic factors contributing to the regenerative failure. However, clinical trials with single treatments will pave the path for future combinatorial approaches to provide meaningful benefits when applied with existing neurorehabilitative and compensatory approaches.

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Neurorehabilitation of the Upper Extremity

22

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Abstract

Individuals with tetraplegia are largely dependent on the support of caregivers and relatives for basic activities of daily living. Therefore, rehabilitation aims at achieving the greatest amount of autonomy in everyday life by achieving a basic grasping function. The therapeutic approaches are categorised into compensatory and restorative strategies: Compensatory strategies include the provision of an active/passive tenodesis grip, splinting, fitting and adjustment of customised tools to compensate for a lost hand function. Restorative therapeutic approaches are based on principles of motor learning and aim at the restitution of the original function. In cases where substantial neurological recovery occurs, it is highly important to regularly adapt compensatory therapies and to rethink the need for technical aids and assistive devices.

Regular assessments are not only needed for objective evaluation of the individual's neurological and functional recovery over the course of rehabilitation but also to obtain information of the patient's skills, needs and own priorities. A comprehensive assessment helps to match rehabilitative and therapeutic possibilities to individual needs of a patient and to provide an optimised therapy.

Triggered by the rapid technological progress, new techniques and devices have been developed over the last years for enhancement of the treatment of upper extremity impairments, such as non-invasive stimulation or complex robotic devices. It needs to be shown in clinical studies involving a substantial number of participants, if these therapies lead to a superior functional outcome compared to or in combination with traditional treatment options.

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22.1 Introduction

Bilateral loss of hand function as a consequence of an injury of the cervical spinal cord results in a substantial dependency of affected persons on relatives and caregivers. This obviously leads to a tremendous reduction in quality of life and restricts full participation in social and professional activities. It is therefore not surprising that individuals with cervical spinal cord injury (SCI) rate an improvement of a missing grasping function as their highest priority [1, 51].

The overall aim of all neurorehabilitative efforts in persons with tetraplegia is to support an individual in achieving the highest possible level of autonomy and independence. To enhance existing skills, regain lost ones or develop compensatory means, and helping the patient to simplify or to set the grounds for everyday and professional life in the first place are the main goals of occupational therapy in particular in the first phase of rehabilitation after onset of SCI. To achieve these goals, occupational therapists make use of a variety of different treatment methods which are closely linked to the individual's neurological situation. Obviously, the therapeutic focus is put primarily on the enhancement of upper extremity motor functions and manipulation skills. However, also the improvement of sensory function, the normalisation of hypersensibility and the prevention or reduction of nociceptive pain or muscular hypertonus represent important components of the therapeutic spectrum in patients with SCI.

The aim of this chapter is to provide an overall overview of the therapeutic aims, concepts and methods used for neurorehabilitation of upper extremity function according to the level and severity of SCI. Two basic concepts are applied in the rehabilitation of individuals with SCI, namely, restoration and compensation including substitution. In a restorative approach, methods based on the principles of motor learning are used for restitution of the original function. In a compensational approach, technical aids and assistive technology are used for substitution of a permanently lost function. Each person needs to be properly characterised in regard to her or his potential of functional capabilities to define specific therapeutic goals and to set up and regularly adapt an individualised therapy regime. This means that regular assessments not only of the neurological and functional status but also of the needs and priorities of individuals with SCI need to be performed. This chapter will list the most widespread assessments applied in individuals with tetraplegia and reports on their advantages and challenges experienced in their routine application. Also, a selection of promising technology-based restorative therapeutic options such as functional electrical stimulation or complex robotic devices will be discussed with regard to their added value for the rehabilitation outcome.

22.2 Characteristics of Individuals with Cervical Spinal Cord Injury

An analysis of the database of the European Multicenter Study about Spinal Cord Injury (EMSCI) [6] shows that approximately 65 % of the tetraplegic patients with traumatic and ischemic SCI have an initial neurological level of C4 (37.9 %) and C5

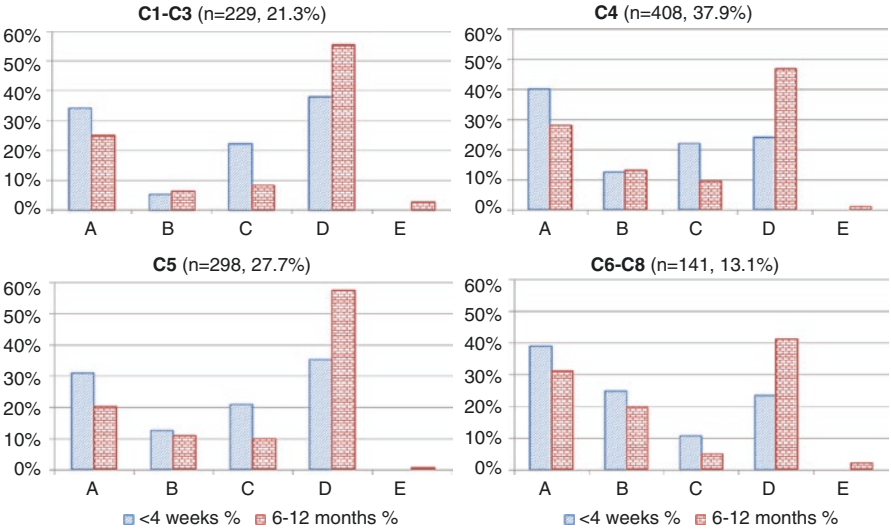

Fig. 22.1 Distribution of the initial (<4 weeks post injury) and chronic (6–12 months post injury) ASIA impairment scale (*AIS*) grades grouped by the initial (<4 weeks post injury) neurological level of injury within a European cohort of traumatic and ischemic SCI (N=1,076 patients)

(27.7 %). About 40 % of the patients with tetraplegia initially have a sensorimotor-complete SCI (ASIA impairment scale (AIS) A [21]). In half of the patients with tetraplegia, residual motor functions are preserved below the level of injury (AIS C and D). These individuals have a high potential for recovery of substantial motor functions over the first year after SCI (Fig. 22.1), with the highest amount of neurological recovery within the first 3 months after SCI [6]. In the chronic stage, 50 % of the tetraplegic patients are classified as AIS D meaning that half or more of their key muscles below the neurological level have a muscle grade equal or greater to three (out of five). Most of these patients suffer from a central cord syndrome (CCS) meaning that the strength of the muscles of the lower extremities is higher than those of the arms [48]. Due to the fact that in CCS a combination of upper and lower motor neuron damage occurs, these patients often have a limited potential for neurological recovery of upper extremity function. They might regain independent ambulation, but may not achieve full upper extremity strength [47].

Three-fourth of the initially sensorimotor-complete (AIS A) patients stay complete. However, they recover on average 10 motor points in their upper extremity motor scores independent from the initial cervical level of injury [28, 52]. An initial motor zone of partial preservation of two segments or more is associated with a gain of two or more motor levels 1 year after SCI [34]. Functional recovery of upper extremity function is significantly greater for those individuals regaining two motor levels compared with those recovering only one or no motor level. This is the case in 22 % of the patients with an initial motor level of C4 and in 27 % of the initially C5 patients [28].

An important factor for the individual prognosis of neurological recovery is the degree of lower motor neuron damage. Although numbers in the literature vary to a large degree, it can be assumed that at least in the high-lesioned patients with a neurological level of injury at or rostral to C4 a substantial degree of denervation in particular of the biceps muscle is present [10, 39]. A thorough neurological examination (reflex testing, neurophysiological nerve conduction recordings) may help to identify the extent of lower motor neuron damage associated to a cervical spinal lesion. The knowledge about the status of innervation of the upper extremity muscles is of utmost importance for selection of the appropriate therapeutic approach (compensation or restoration) and to align patient's expectations for recovery with realistic rehabilitation goals based on clinical experience. Additionally, an agonistic/antagonistic imbalance of innervation may result in a higher risk for joint contractures, if not adequately treated [4].

22.3 Restoration Versus Compensation: The Two Ends of a Therapeutic Continuum

The basic aim of rehabilitation of upper extremity function in subjects with tetraplegia is to provide them with as much autonomy as possible. A strong focus is put on the ability to perform activities of daily living such as dressing/undressing, personal hygiene, eating or performing transfers independent from caregivers. In this context, training is based on two fundamental principles, namely, restoration or compensation.

Assuming that an SCI leads to the loss of skilled motor behaviour, recovery or restoration would depend on the reacquisition of elemental motor patterns by motor learning or, in the absence of reacquisition, adaptation of remaining (compensation) or integration of alternative (substitution) motor elements. The term *recovery* of motor performance is defined as the restoration of elemental motor patterns present prior to central nervous system (CNS) injury [32]. Motor *compensation* is defined as the appearance of new motor patterns resulting from the adaptation of remaining motor elements or *substitution*, meaning that functions are taken over, replaced or substituted by technical aids or assistive devices.

There is still a lack of consensus on the definition of "functional recovery". This term is often used without distinguishing whether the "recovery" is occurring at the body function/structure or the activity level. Thus, there is often no consensus about whether "recovery" is because of true motor recovery or compensation at each of these levels.

The International Classification of Functioning, Disability and Health (ICF [53, 54]), published by the WHO in 2001, provides a standard language and framework for the description of health and health-related states independent from specific diseases. Functioning and disability are viewed as a complex interaction between the health condition of the individual and the contextual factors of the environment as well as personal factors. The ICF is based on a biopsychosocial model and provides a coherent view of different perspectives of health: biological, individual and social. It is structured around the following broad constructs:

- Body functions and structure
- Activities (related to tasks and actions by an individual) and participation (involvement in a life situation)
- Environmental factors

In an attempt to improve knowledge exchange between fundamental researchers, clinical researchers and clinicians, a definition of recovery and compensation at three different levels of the ICF, at which each may occur, has been proposed (Table 22.1).

A way of distinguishing between *recovery* and *compensation* is to look on how the movement is performed (body function/structure level) and on the movement outcome (activity level). At the body function/structure level, the emphasis is on the quality of movement regardless of movement outcome or task accomplishment. Recovery at this level is characterised by the reappearance of pre-injury movement patterns during task accomplishment. True motor recovery at this level, therefore, could be characterised, for example, by a decrease in spasticity or by a reduction in trunk displacement during a reaching or pointing movement. *Adaptive compensation* at this level would be characterised by the appearance of alternative movement

Table 22.1 Definitions of motor recovery and motor compensation at three different ICF levels

Level	Recovery	Compensation
ICF: health condition	*Restoring function in neural tissue that was initially impaired after injury*. May be seen as spontaneous reactivation of spinal axons, interneurons or motor neurons affected by the spinal trauma	*Neural tissue acquires a function that it did not have prior to injury*. May be seen as activation of alternative spinal cord or brain areas normally not observed in able-bodied individuals
ICF: body function/ structure (performance)	*Restoring the ability to perform a movement in the same manner as it was performed before injury*. This may occur through the reappearance of pre-injury movement patterns during task accomplishment (voluntary joint range of motion, temporal and spatial inter-joint coordination, etc.)	*Performing an old movement in a new manner*. May be seen as the appearance of alternative movement patterns (i.e. recruitment of additional or different degrees of freedom, changes in muscle activation patterns such as increased agonist/antagonist coactivation, delays in timing between movements of adjacent joints, etc.) during task accomplishment
ICF: activity (functional)	*Successful task accomplishment using limbs or end effectors typically used by non-disabled individuals*[a]	*Successful task accomplishment using alternative end effectors such as neuroprostheses or robot arms*

Adapted from Levin et al. [32]

[a]Note that task performance may be successful using compensatory motor strategies and movement patterns

patterns during the accomplishment of a task. *Substitutive compensation* would reflect the use of different effectors to replace lost motor elements. It should be recognised that both adaptive and substitutive compensation may occur in various combinations at the performance level. An example of adaptive compensation is the use of excessive shoulder abduction when the range of active elbow extension is decreased. At the level of the wrist and hand, alternative grasping strategies such as anchoring the fingers on the object to achieve a passive grasp can compensate for the lack of active finger flexion.

Recovery at the activity level requires that the task is performed using the same end effectors and joints in the same movement patterns typically used by able-bodied individuals. In contrast, compensation at this level often takes the form of substitution and would be noted if the patients were able to accomplish the task using assistive devices.

The question of course arises, when to apply a restorative therapy approach and when to move to a compensatory training or vice versa? There is no general answer to these questions, and the separation of compensatory from restorative therapies is often difficult or even impossible. As a general rule, in the first 3 to 6 months after the injury, where the potential for neurological recovery is highest, the focus of rehabilitation specialists is on transferring neurological recovery into functional improvements by application of restorative therapy approaches. However, in parallel in some patients, compensatory movements or substitutive technical aids may be encouraged from the very beginning to maximise functional ability. This is in particular true for patients with severe impairment, poor prognosis and likely low benefit from restorative therapies. Of course, if unexpectedly a patient recovers a substantial amount of sensory or/and motor functions, restorative therapies may be applied at any stage. At the point in time, when only little neurological recovery occurs and the time of admission into the home environment comes close, the more compensatory therapies are in the focus to achieve the highest level of functional ability as a prerequisite for leading an independent life at home.

It is important to emphasise that compensation and recovery are not mutually exclusive. Instead, functional recovery is often dependent upon compensation, and compensatory approaches might enable new possibilities for restorative trainings, e.g. a hand stabilisation orthosis or a grasp neuroprosthesis may allow for retraining shoulder and elbow movements. Because there is no general rule for focusing on compensation or restoration, it is important to know the patient's individual priorities and her or his social environment. Taking them into account is mandatory to agree upon realistic rehabilitative goals and to work with the appropriate therapy methods to achieve them.

22.4 Injury-Level-Dependent Goal Setting

A complete SCI (AIS A) is defined by the absence of motor and sensory functions in the most caudal segments S4/S5 [21]. However, in reality this means that in most of the patients with complete cervical SCI, there is only a limited zone of partial preservation of one or two segments below the neurological and/or motor level of injury.

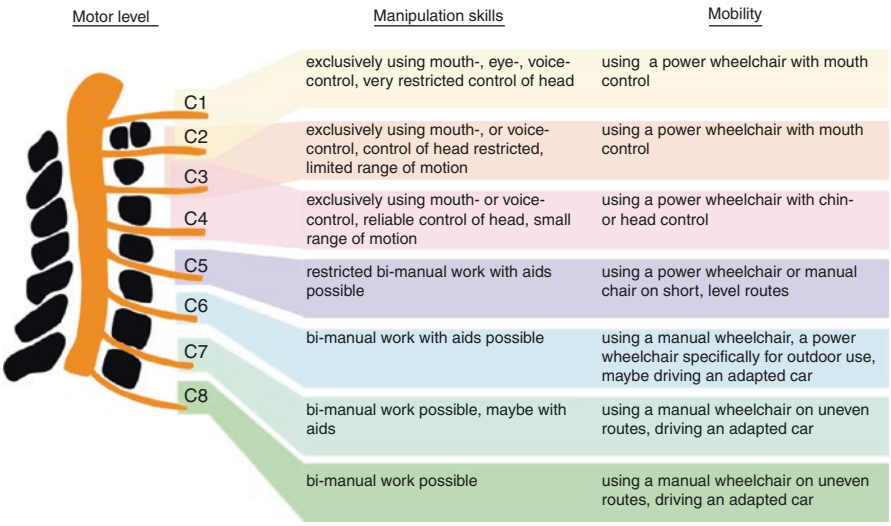

Fig. 22.2 Overview of goals for achievable manipulation skills and level of mobility in respect to the cervical motor level (Adapted from Gerner [11])

For patients with cervical SCI a shift of the motor level of only one segment caudally can result in a tremendous improvement in independence. Taking additional factors like age, pre-injury comorbidities and diseases or cultural background not into account, general rehabilitative goals can be defined in respect to the motor level (Fig. 22.2). The initial setting of goals is important to bundle all rehabilitative efforts and for communication to the patient.

22.4.1 Goal Setting in Complete Tetraplegia

With a motor level between C0 and C4, an individual with tetraplegia is not able to achieve a high level of autonomy and to act independently without technical aids and appliances and personal assistance. In particular, persons with a motor level rostral to C4, who may be dependent on artificial ventilation, need a very high level of support by caregivers. The general rule applies that the higher the neurological level and the severity of the lesion, the more electronic aids are being used to achieve at least a minimal level of autonomy. In cases of minimal residual functions, therapy is strongly focused on the development of individual solutions and the adaptation of different aids and appliances to achieve the highest level of autonomy possible. This includes aids to control a wheelchair for mobility and a computer to get access to information and to communicate to the outside world.

The residual motor functions present in the case of a motor level of C5 are normally sufficient to achieve a certain degree of autonomy in the sense of independence from caregivers for at least most of the day. Substitutional approaches consist of the individual adaption of an electrically powered, electrically assisted or manual wheelchair and the provision of simple aids such as holders for pens, razors, etc.

Compensatory therapy focuses on the development of an active or passive tenodesis grip (Figs. 22.3 and 22.4). Restorative therapies are performed with the aim of strengthening shoulder and upper arm muscles and maintaining the mobility of the joints of the upper extremities.

A full control of the wrist extensor muscles (extensor carpi radialis muscle) enables patients with a motor level of C6 to achieve a higher degree of autonomy than patients with higher SCI. Compared to a patient without active wrist extension, the need for technical aids and appliances is reduced. The major aim of rehabilitation in this patient group is to strengthen the wrist extensors to achieve together with a shortening of the finger flexor muscles a strong grasp. This active tenodesis grip may be used by patients very effectively. With a motor level of C6, a patient is basically able to lead an autonomous life independent of the help of others by using adequate aids and appliances.

Fig. 22.3 Basic principle of the passive tenodesis grip. A supination of the wrist leads to a passive wrist extension and closing of the fingers

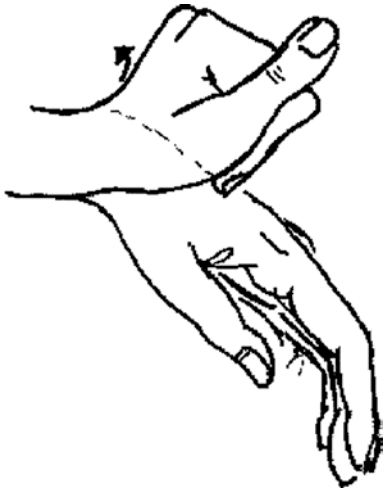

Fig. 22.4 Basic principle of the active tenodesis grip, where an active wrist extension results in a passive closing of the fingers

In motor levels at or caudal to C7, there is active control over the triceps brachii muscle, which allows for the active extension of the elbow. In this subpopulation, technical aids and appliances can be reduced to a minimum. Due to the active control of the elbow flexors and extensors, a better fine motor control and a more precise and faster placement of the hand in space are possible. Additionally, a better weight relief for prevention of pressure injuries can be performed by the individual with SCI. In this group of patients, also partial control of hand muscles may be preserved to a certain degree to support hand opening or closing. Like in all other groups, a strong focus of all restorative therapies is strength training of all muscles under voluntary control.

In patients with a motor level of C8, more hand and finger movements are present, meaning that no compensatory approaches such as the development of a tenodesis grip need to be applied. Here, mostly restorative therapies are in the focus to increase strength and improve coordination.

Apparently, the segmental innervation is not restricted to the key muscles mentioned so far but also includes other muscles, which also substantially contribute to a better functional status resulting in a higher level of autonomy and in the ability to lead a more independent and self-determined life.

22.4.2 Goal Setting in Incomplete Tetraplegia

In patients with incomplete tetraplegia, the setting of goals dependent on the lesion level is impossible on a general level due to the heterogeneity of this patient population. The sensory and motor impairments of the upper extremity in incomplete lesions normally differ to such a large degree that a highly individualised goal setting is necessary resulting in a variety of different treatments. Restorative therapies concentrate on strength training of muscles under full or partial voluntary control, maintaining the passive and active range of movement, reduction of spasticity and improvement of coordination. The latter aims at practising the physiological motion sequence in a repetitive manner and translate this into activities of daily living. The methods are basically the same than those used for therapy of individuals with complete cervical SCI. A combination of restorative and compensatory approaches might be used to achieve a maximum of independence.

22.5 Compensatory and Substitutional Therapeutic Strategies

In the absence of the possibility for reacquisition of pre-injury motor behaviours in very severely impaired individuals or at the chronic stage of injury, adaptation of remaining (compensation) or integration of alternative (substitution) motor elements are considered as the primary therapeutic approach. The main common compensatory strategies in persons with cervical SCI are the establishment of a

passive or active tenodesis grip [14] and provision of dedicated tools and adaptation of the environment to enhance independence in everyday activities.

22.5.1 Passive and Active Tenodesis Grip

A tenodesis grip represents a passive hand grasp mechanism effected by wrist extension. It is caused by the anatomical constraints of the finger muscles in particular of the finger flexors, which as two joint muscles cross the wrist joint and develop a passive tension during wrist extension. This passive tension might be sufficient to accomplish a functional grasping task, if the fingers and the thumb are in a certain alignment to each other. If the wrist is put in flexion position, the fingers will straighten and release a grasped object.

The tenodesis grip can be either passive or active. In the passive condition, wrist extensor muscles have a strength below grade 3, and closing of the hand is only possible passively by supination of the hand and thereby making use of gravity to extend the wrist (Fig. 22.3). Hand opening is achieved by pronation and passive wrist flexion. A prerequisite for an active tenodesis grip is a strength grade of the extensor carpi radialis muscle of at least 3, which is then capable of actively extending the wrist (Fig. 22.4).

Due to high importance, measures for the development of a tenodesis grip are initiated very early in the rehabilitation process of patients who are likely to recover a strong wrist extension. A major component of the therapeutic approach is appropriate splinting of the fingers and wrist to achieve a shortening of the finger and thumb flexor muscles [26]. In order to achieve an optimal outcome, care must be taken to avoid shortening of extensor muscles resulting in extended fingers unable to grasp anything as well as the shortening of the collateral tendons of the hand and finger joints, which results in a non-physiological hand and finger posture. The shortening of muscles is in contrast to contractures of joints reversible by the consequent application of stretching procedures.

Although widely used, there is still no consensus about the general effectiveness of splinting and the superiority of different splinting methods. However, it seems that in the chronic phase splinting might not have the expected effect [15].

In the chronic stage, a tenodesis grip can be surgically installed by the use of tendon transfers in combination with arthrodesis and/or tenodesis procedures [17]. As an example, an active tenodesis grip might be achieved by the transfer of a strong brachioradialis muscle to the distal tendons of the weak carpi radialis muscle together with a tenodesis for synchronisation of all finger flexor tendons (Zancolli lasso procedure). Depending on the number of strong active muscles distal to the elbow, also a higher level of dexterity of finger and hand movements might be achieved.

22.5.2 Assistive Devices and Adaptation of the Environment

Even with an active tenodesis grip, the fingers are closing only passively resulting in a low grasp force [18]. To enable patients to cope with the challenges of daily

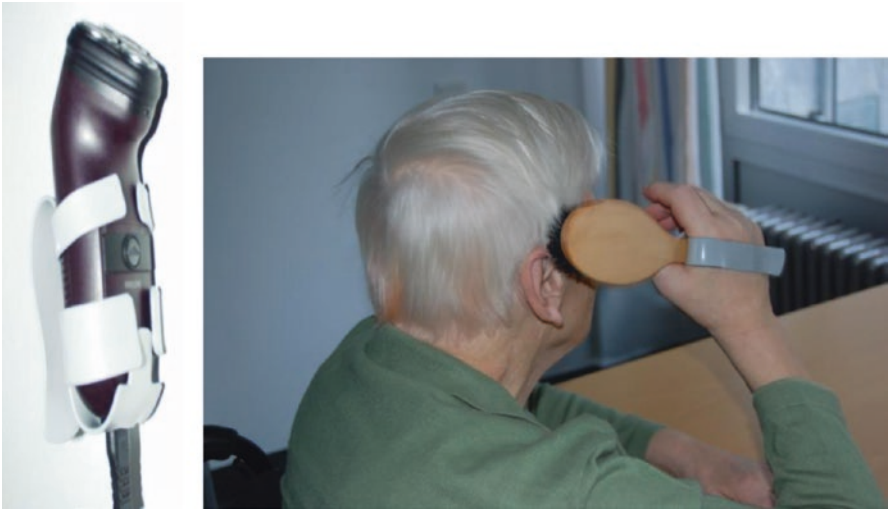

Fig. 22.5 Examples for adaptation of everyday items for enabling patients to perform activities of daily living such as grooming or self-care

living, adapted tools are provided. This includes, but is not restricted to, clamping holders for razors, hairbrush, toothbrush, silverware, etc. (Fig. 22.5).

In patients who do not achieve complete autonomy, the counselling of patients and family members, for example, regarding aids and appliances or the modification of the home environment forms is an important part of rehabilitation. An early involvement of family members and a thorough familiarisation with the operation of assistive devices ensure the optimal support after in-patient rehabilitation. The entire selection of medical aids and appliances is strongly depending on a variety of factors such as the patient's domestic and professional situation, the marital status, age and also pre-existing comorbidities.

The fast growing number of smart homes with remote or internet-based control of light and heating control, door opener or other electronic devices helps patients to achieve some part of autonomy without the need for additional expensive installations. Also the traditional voice control of mobile phones allows patients a self-initiated communication with relatively inexpensive equipment. It can be expected that following the idea of universal design, more devices may be operated by persons with tetraplegia in the future.

22.6 Restorative Therapeutic Strategies

A recent review on the effectiveness of restorative therapies came to the conclusion that training including exercise therapy and (functional) electrical stimulation of the upper limb following cervical SCI leads to improvements in muscle strength, upper-limb function and activity of daily living resulting in a better quality of life [33]. Some studies in the literature indicate that early initiation of SCI-specific

rehabilitation is extremely important. A delay in starting these interventions may negatively influence ultimate functional capability [22, 43]. On the other hand, this does not mean that training initiated in the chronic stage does not result in improvements of muscle strength, of upper extremity function and consequently of activities of daily living or quality of life, but the effects are most probably smaller. Therapeutic exercises may have different aims in patients with tetraplegia, among them training of muscular strength and endurance, relaxation of muscles with increased muscle tone, reduction of upper-limb edema, maintenance of joint mobility and flexibility by moving limbs in their entire range of movement and improvement of coordination and fine motor skills by task-specific, goal-oriented, high-intensity training regimes.

22.6.1 Strength Training

One important prerequisite for functional restoration is to exercise weak muscles in order to strengthen them and provide the basis for their appropriate integration into relevant movements. This is mainly done with active-assisted and active-resistive exercises:

- *Active assisted* – Patients who are not able to fully perform a desired movement are supported by therapists during different phases of the movement execution as well as over the whole range of motion. The therapists normally work on an assist-as-needed basis meaning that the therapist provides only the minimal amount of support to successfully complete the task. The intention is to challenge the patient, but not to cause frustration. An important issue is to guide the movements of a patient on a physiological trajectory, so that trick movements and herewith training of already stronger muscles are avoided. In active-assisted strength training, often gravity-eliminating systems providing a sling-based weight support of the forearm (e.g. Swedish Help Arm produced by different manufacturers) are used. With the help of this device, patients can put their focus on the quality and repetition of the different movements necessary in daily life without excessive muscular fatigue.
- *Active resistive* – If a patient is able to complete the desired movements over the whole range of motion, an adapted amount of resistance to the movement is given by a therapist either for more effective strength training or for guidance of movements. Resistance-based training can be done unilaterally as well as bilaterally.

Electrical stimulation may also effectively contribute to upper-limb muscle and in particular wrist extensor strength [12, 13, 24, 41]. However, electrical stimulation should be integrated into a comprehensive occupational therapy regime to transfer the increased muscular strength into functional improvements like self-feeding abilities [24].

22.6.2 Use of Motor Learning Regimes Including Rehabilitation Robotics

The fundamental concept of restoration of motor functions is based on the assumption that practice of task-specific movements induces plastic changes in the altered CNS representing the structural correlate of motor learning. Moreover, the frequency and duration of practice correlates with the level of improvement of motor performance. Thus, repetition represents the key factor for successful motor learning. Although this may be the most effective way to improve short-term performance during the training session, it is not sufficient for retaining motor skills over time. A set of factors – called principles of motor learning (Table 22.2) – have been identified that contribute to the long-term retention of a newly acquired skill [27].

Among the principles of motor learning are the degree of active participation and motivation of the patient, an appropriate intrinsic and extrinsic feedback, the

Table 22.2 List of "principles of motor learning"

Principle of motor learning	Explanation
Task specificity	To improve a specific skill, the respective movement task or closely related needs to be practised
Active participation	Active participation of the patient forms the basis for initiation of neuronal plastic changes. Motivation and eagerness strongly influence the therapy outcome
Repetition	For transfer short-term adaptations in motor control into sustained movement patterns, the movement task has to be repeated often. It must be emphasised that the task has to be repeated often and not the movement
Adaptation of the complexity ("shaping")	The difficulty of a movement task has to be chosen according to the functional status of the patient. A too simple movement task is boring and thus does not challenge the patient; a too complex, not executable task is overloading the patient and is therefore frustrating
Feedback	Inherent as well as augmented feedback of the motor performance forms an essential component of a therapy for normalisation of pathological movement patterns
Variability "contextual interference"	Whereas repetition of the same movement task leads to an increased performance of the trained movement, the introduction of variability enhances the learning process and retention. Diversification increases the active participation of a patient
Distributed practice	In general, shorter, distributed sessions with intermittent pause periods seem to be more effective than longer block sessions ("massed practice")
Generalisation	Improved motor skills in an artificial environment, e.g. treadmill or locomotion robot, do not necessarily lead to enhanced skills in a natural environment. Dedicated therapeutic interventions are needed to transfer training skills to daily life activities

Fig. 22.6 Devices for a shaped manipulation training: large and light-weighted objects (*left*) are used in the beginning of rehabilitation, which in case of neurological improvements are exchanged by smaller (*right*) and also heavier objects

adaptation of the complexity of the movement task and the contextual interference, in which variability and diversification of the movement tasks are explicit components of the training.

In a task-specific grasping training, difficulty of the therapy is adjusted to the skills of the patients. Normally therapy starts with light and large objects, which can be manipulated more easily and provide the patient a positive feedback thereby leading to a higher motivation. To shape the therapy to the skills of the patient, increasingly heavier and smaller objects are used over the course of rehabilitation (Fig. 22.6). In the end, the difficulty level can be increased by providing additional resistance with objects applied with Velcro.

22.6.2.1 Robotic and Electrical Stimulation-Based Training Approaches

Robotic systems may serve as useful adjuncts in restorative therapies based on the principles of motor learning. They contain active or passive elements that support the weak movements of the users and therefore lead to a higher number of task repetitions. All of the robotic devices contain sensors for real-time measurement of joint angles and allow for their feedback to the user. The measured kinematic parameters can be used to control a variety of virtual motor tasks on a computer screen. The big advantage of this virtual training setting is the possibility for adaptation of the difficulty level to the residual motor functions of a user. By this, users not able to perform a real task can be enabled to perform a virtual task, which is highly motivating for a patient to actively participate in the training.

Robotic training devices are an emerging technology and have not yet been widely used in the clinical rehabilitation setting. Therefore, there is no sufficient evidence for their superiority to traditional therapy regimes. In contrast, most of the reviews on the clinical use of robotic devices come to the conclusion that robotic therapies are not superior to treatment as usual, if both are applied with the same intensity [42].

However, the term “robotic” is not precisely defined, so that the results of studies cannot be easily compared with each other. All of the devices called “robotic” have

in common is that they provide some sort of feedback to the user about her or his current kinematics of joints or upper extremity segments.

But some of the devices are only based on passive, mainly spring-based actuators meaning only capable of providing a predefined amount of weight support independent from the position of the upper extremity. In order to call an assistive device "robotic", it needs to integrate electric or pneumatic drives to actively support the movements of a user. Even then there are two different approaches to support patients' movements, which are (1) an end-effector-based approach, in which the hand is moved mostly in a horizontal plane by a driven "knob", or (2) an exoskeleton-based approach, in which the kinematics of each joint is supported independently. In end-effector-based devices, there is no need for alignment of technical to anatomical joints, which facilitates a fast and easy setup. However, a dedicated movement can only be trained by supervision of a therapist, who provides the patient with the correct instructions avoiding compensational movements. Upper extremity exoskeletons provide the possibility for dedicated support of each upper extremity joint in particular the shoulder, but their correct placement is challenging and time-consuming (Fig. 22.7).

In the therapy of stroke, a recent randomised controlled trial provides evidence that robotic therapy with an actively driven complete upper extremity exoskeleton results in a slightly better outcome compared to traditional therapy of the same intensity [23].

Although safety and feasibility studies of some active robotic devices exist [5, 55, 58], efficacy trials involving a substantial number of study participants with SCI are missing. Only very limited evidence from randomised controlled trials is available indicating that the use of a feedback-based weight support system (Armeo Spring, Hocoma, Volketswil, Switzerland) does not lead to a superior outcome compared to a conventional occupational training of the same intensity [59].

Another possibility to facilitate motor learning is the use of non-invasive functional electrical stimulation. Electrical stimulation activates innervated muscles by short-current impulses, which are mostly applied by self-adhesive electrodes placed on the skin (for more details, see Chap. 24). The stimulation intensity and activation

Fig. 22.7 The seven degrees of freedom upper extremity rehabilitation exoskeleton Armeo Power (with permission from Hocoma, Volketswil, Switzerland)

patterns of electrodes on the arm and hand can be adjusted in a way that a grasping and reaching function can be restored. Electrical stimulation thereby supports a task-specific training and generates a rich afferent feedback to the CNS, which may contribute in particular in the early phase of rehabilitation to a better neurological and functional recovery. There is some evidence from two studies that a combination of electrical stimulation with conventional occupational therapy alone is more effective in improving grasp force, upper extremity function and activities of daily living than conventional therapy alone [20, 25, 45, 46]. Most importantly these gains were maintained at 6 months follow-up [20]. Controversially, other studies showed no extra benefit, and it seems that electrical stimulation does not enhance fine motor control abilities [16, 25, 46]. In general, more well-designed, randomised controlled studies are needed with higher sample sizes to see if the results can be generalised to other patient populations and rehabilitation settings.

22.6.3 Restoration of Sensory Functions

An SCI is not only associated with a loss of motor but also of sensory function. The loss of sensory function includes the inability to feel touch, temperature, pain or joint and limb position. The loss of proprioception represents a severe confounding factor for restorative therapies in particular during the first phase of rehabilitation. Even if patients have preserved motor functions allowing them to grasp and manipulate objects, but have no sensation of their grasping force, they have to compensate the loss of hand sensitivity with visual control. Another important issue is that patients need to take care about their trunk posture, because only a stable sitting position allows for the effective use of the residual motor functions of the arms in everyday life.

In a situation where no touch sensation or proprioception is preserved, it is very hard to train sensation. However, if a certain degree of sensation is preserved, different stimuli are used to specifically activate different type of exteroceptors. For this purpose, different materials or materials of different temperatures are used to brush over the patient's skin with different levels of pressure. The patient is instructed to close the eyes and to concentrate on the sensation caused by the material while giving feedback about the location of the touch on the body. This exercise requires a high level of concentration from the patient and is thus restricted to a period of time of a maximum of 10–15 min. Assessment such as the light touch or two-point discrimination tests can be applied during the therapy to check for changes in sensory perception.

Somatosensory electrical stimulation of the median nerve with intensity set below motor threshold may be beneficial in improving sensory function when applied as an adjunct to massed practice of task-oriented skills training programmes [2]. Also, the rubber hand illusion therapy used in hand prosthetic users to treat neuropathic pain seems to improve the sensory perception, although the available evidence is based on a small number of subjects with cervical SCI [30].

22.7 Therapeutic Challenges

In general, the rehabilitation of persons with SCI is sometimes very challenging, independent of the severity of the impairments, and therapeutic possibilities may be limited resulting in a poor outcome. Over the last two decades, there is a shift in the SCI population, at least in industrial countries [44], from young, traumatic towards older, non-traumatic patients having more comorbidities. This leads to the consequence that therapeutic aims need to be carefully aligned to the status and the constraints of each individual. It may happen that older patients with pre-injury diseases such as arthritis or diabetes may not achieve the theoretically possible rehabilitation goals. Older patients often have attention and concentration deficits that restrict the adherence to therapies and instructions of therapists. Additionally, older people tend to have more reservations against electronic aids or technical equipment in general, which result in longer training times and higher level of frustration in both patients and therapists.

Another confounding factor of successful functional upper extremity rehabilitation is severe spasticity. Spasticity and the associated increased muscular tone may lead to non-physiological joint positions, which may as a consequence prevent a tenodesis grip, may lead to nociceptive pain or may not allow for a stable sitting position. Severe spasticity interfers with training efforts and results in a lower degree of independence. Besides spasmolytic medication, passive stretching might have a positive influence on spasticity. On the other hand, light to moderate spasticity prevents muscular atrophy. Sometimes spastic movement patterns can be voluntarily triggered by the patient who may use them effectively for activities of daily living. Therefore, a careful evaluation of the patient's status needs to be performed to initiate the appropriate therapies.

An imbalance between innervated agonistic and denervated antagonistic muscles such as hypertonus in the biceps muscle and a flaccid triceps muscle might lead to a contracture of the elbow joint in flexion position [4, 8]. This does not only restrict the use of the hand and limit independence but additionally represents a challenge for proper (self-)care and personal hygiene. Appropriate positioning of the upper limb and the shoulder together with passive movements and muscle stretching may prevent the development of contractures or at least may preserve an acceptable status [26].

A common and widespread problem in patients with tetraplegia is shoulder pain. The weaker the shoulder muscles, the higher the risk for developing a (sub)luxation and the associated pain in the exclusively muscular-stabilised shoulder joint. It is important to consequently educate the patient, the caregivers and the whole rehabilitation team to avoid mechanical overload or muscular stress to the shoulder which might result in restrictions in activities of daily living [7, 36]. Besides an adequate positioning, stabilising tapes on the shoulder, massage or electrical stimulation might reduce the nociceptive pain.

One of the most challenging secondary complications with a high negative impact on quality of life is the presence of neuropathic pain, which in severe cases

render any rehabilitative therapeutic effort impossible. Effective therapies for the treatment of severe neuropathic pain are still missing (see also Chapter 12).

On an individual basis, it is sometimes challenging to decide when to decrease the intensity of restorative therapies and to shift to compensatory training or substitution of lost functions by technical aids. This particularly applies to the development of the tenodesis grip. During splinting it is very important to control for recovery of hand and finger muscles to shift back to a restorative therapy approach by training of the intrinsic hand muscles. While to a certain extent standard therapeutic procedures are existing for patients with complete cervical SCI, no definitive rules are present for the treatment of incomplete patients or patients with a substantial zone of partial preservation below the level of lesion.

Additional to all physical factors restricting the rehabilitative efforts, there is the human factor that a newly spinal cord injured person needs to psychologically adapt to the new situation. It is often challenging to motivate especially older patients to become an active part in therapies in the very early period after SCI. On the other hand, the first 3 months after SCI are the most effective period for neurological recovery and restoration. Therefore, goal-oriented therapies need to start early, in particular in the light of the fact that the time for in-patient rehabilitation has significantly decreased over the last two decades.

22.8 Assessments in Daily Routine and Their Clinical Consequences

Regular assessments are not only needed for objective evaluation of the individuals' neurological and functional recovery over the course of rehabilitation but also to obtain information of the patients' skills, needs and priorities. A comprehensive assessment helps to obtain the individual needs of a patient and to match rehabilitative and therapeutic possibilities. Assessments are important to define an initial treatment regime and to provide an optimised therapy in particular regarding restorative or compensatory approaches. The analysis of outcome measures on a subgroup level of individuals with comparable initial neurological statuses allows healthcare professionals to quantitatively describe, predict and evaluate the neurological recovery in order to provide benchmarks for individuals with SCI. Assessments are also important to communicate the status and progress of a patient to the multidisciplinary team members.

As a summary, assessments support clinicians in their daily routine by providing:

1. Prognostic information by means of an early assessment after injury
2. Allow for individually tailored rehabilitation plans (i.e. compensatory versus restorative approaches, adaptive equipment need)
3. Short-term therapy planning (force training versus coordination, etc.)
4. The ability to evaluate the success of rehabilitation interventions

As mentioned before, the International Classification of Disability and Functioning (ICF) provides a coherent view of different perspectives of disability regarding "body functions and structures", "activities", "participation" and "environmental factors". There is consensus that for a comprehensive description of an individual's condition, assessments related to all these domains are necessary. However, in contrast to assessment schemes applied in research studies, routine examinations in the clinical environment need to comply with different demands: They should be focused on the most essential information relevant for clinical decision-making and should be able to be conducted in a short amount of time. During the initial in-patient phase, the therapeutic focus is on "body function and structures" and "activity" and so are the assessments.

For selection of the appropriate therapies, it is highly important to know if an improvement in activities results from neurological recovery or if it is based on better compensatory skills. Therefore, the distinction between clinical impairment and function measures needs to be made. Impairment scales focusing on body function and structures measure specific motor aspects that may limit but are not related to task accomplishment (spasticity, strength, isolated joint motion), whereas functional scales measure the task success on an activity level (key turning, jar opening, i.e. functional gains). However, functional gains can occur even in the absence of motor recovery, i.e. lost motor patterns have not returned. Most evaluations at the activity level neither specify how the task is accomplished nor which compensatory movements were used in place of motor patterns observed in non-disabled individuals. Difficulties arise in interpretation of such functional tests to indicate recovery because scores on these tests may improve either when the intervention results in improvements in motor patterns or in increasing compensations and the distinction between them is not made. An example of a relatively new scale that attempts to incorporate both measures of task success as well as movement quality during task accomplishment is the Wolf motor function test [2, 56] that is more often used for the documentation of stroke survivors than in individuals with SCI. More tests of this type that provide an appreciation of movement quality are needed in rehabilitation to better distinguish between motor recovery and compensation at the activity level.

22.8.1 Clinically Relevant Upper Extremity Assessments in SCI

In the next subchapters, an overview of the assessments most relevant for the documentation in the clinical environment is presented. The following compilation (Table 22.3) does not claim to be exhaustive but rather represents an attempt to list the common examinations typically used in in-patient rehabilitation.

22.8.1.1 Assessments on Body Function and Structures

For clinical decision-making, a thorough knowledge of the individual musculoskeletal and neurological status is mandatory at every stage of rehabilitation. The

Table 22.3 Overview of assessments relevant in the clinical environment and associated ICF categories

Body function and structure	Activity	Participation
GRASSP		Canadian Occupational Performance Measure (COPM)
Reflex status	Capabilities of upper extremity (CUE)	
Two-point discrimination test	Grasp and release test (GRT)	
Range of motion (ROM, neutral-0-method)	Nine-hole peg test	
Manual muscle test	Van Lieshout test short form (VLT-SF)	
Hand force measurement	Spinal Cord Independence Measure (SCIM) III	
	Occupational therapy assessment	

examinations should provide information about touch perception, strength, reflexes and passive and active joint range of motion.

In particular in the initial phase of rehabilitation for proper prognosis of the degree of recovery and for deciding on the appropriate therapeutic focus (restoration vs. compensation), a thorough knowledge about the degree of denervation is absolutely necessary. While neurophysiological assessments such as needle EMG or nerve conduction velocity measurements provide objective quantitative information, they are time-consuming, rely on expensive equipment not available in all institutions and are hard to integrate into clinical routine examinations mainly performed by therapists. To still be able to gain some insights into the degree of denervation, a testing of the reflex status of the upper extremities is recommended. There are mainly three reflexes, namely, the biceps, supinator and triceps reflex associated with the spinal segments C5 to C7. If reflexes are absent or impaired after the spinal shock phase, there is a high likelihood of denervation of motor neurons at the respective spinal level.

Additionally to the International Standards for the Neurological Classification of Spinal Cord Injury (ISNCSCI) with its dermatome-based examination of light touch and pinprick sensation, the two-point discrimination test is recommended for classification of impairments of touch sensation in patients with partly preserved sensory function. It determines the minimal distance at which a patient can discriminate between being touched with one or two points. The patient's vision is blocked during the examination and the skin area of interest is being pinned. If the patient is able to discriminate between two points with a distance of <6 mm, then the two-point discrimination is considered to be normal, 6–10 mm is rated as fair and a distance between 10 and 15 mm is considered to be poor. Although being a rather gross classification, the two-point discrimination test might be used to access the effects of therapeutic interventions focusing on facilitation of recovery of sensory function.

Testing of the active and passive range of motion of the finger, hand, elbow and shoulder joints represents an essential examination for assessing weakness of muscles, the degree of muscular tone and the integrity of joint structures such as capsules or tendons. A regular ROM assessment helps to identify the risk of developing joint stiffness and to early initiate stretching procedures. It is normally performed together with a manual muscle test for assessment of the strength of upper extremity muscles. The manual muscle exam should not only include the ISNCSCI key muscles, which were selected on the basis of their innervation from only two spinal segments, but also muscles that are more relevant for performing everyday activities.

An instrumented measurement of the overall hand grasp force forms an important component of strength assessments, because of its relevance for performing everyday activities. The test can be performed by dynamometers keeping in mind that devices designed for assessment of forces in the able-bodied population might not be sensitive enough to measure the low forces of patients with tetraplegia. Care must be taken to properly position the dynamometer in the hand to achieve a high reliability and reproducibility of the assessment.

An assessment that covers aspects of body function and structures together with activity is the Graded Redefined Assessment of Strength, Sensibility and Prehension (GRASSP) [19]. The GRASSP was specifically developed as an impairment measure for the upper limbs in tetraplegia and consists of three subcategories: strength, sensation and prehension. It results in five numerical scores that provide a comprehensive profile of upper-limb function. Administration time is estimated between 45 and 90 min. Strength is assessed by a manual muscle test which extends the five ISNCSCI key muscles test by another five muscles important for hand function. Semmes-Weinstein monofilaments are used for testing three palmar and three dorsal key sensory points. Prehension is divided into ability (cylindrical, lateral key and tip-to-tip pinch grasp) and six performance tasks (pour water from a bottle, open jars, pick up and turn a key, transfer pegs, pick up four coins and place in a slot and screw four nuts onto bolts). A full GRASSP was found to demonstrate excellent reliability and construct and concurrent validity for individuals with tetraplegia. It is to be expected that the GRASSP will evolve to a standard assessment of upper extremity function in subjects with tetraplegia due to SCI during all stages of clinical rehabilitation and also in research studies.

22.8.1.2 Assessments on Activity

There is a general consensus that generic hand function tests are too limited for individuals with tetraplegia and therefore are not appropriate [38]. Accordingly, several SCI-specific assessments for the upper extremities have been developed:

The Capabilities of Upper Extremity (CUE) has two variants, a questionnaire (CUE-Q) and a performance test (CUE-T). CUE-Q is a measure of functional limitation in tetraplegia, which can be administered by clinicians in interview format. It takes about 30 min to complete. CUE-T is an objective standardised assessment of upper-limb capabilities specifically developed for persons with tetraplegia [35]. The

16 unilateral and 2 bilateral items were derived from CUE-Q. It takes approximately 45–60 min to conduct this reliable and valid test.

The Grasp and Release Test (GRT) was specifically developed to assess hand opening and closing to be used as a functional test with neuroprostheses. GRT assesses the ability to pick up, move and release six different objects using a palmar or lateral grasp. It takes approximately 20 min to conduct. Two studies reveal that GRT has excellent reliability and adequate to excellent validity [40, 57].

The nine-hole peg test was developed to quantify fine hand motor skills [37]. It consists of a square board with nine holes in it, which are spaced 3.2 cm (1.25 in) apart. The nine wooden pegs should be .64 cm (.25 in) in diameter and 3.2 cm (1.25 in) long. The task is to pick up the pegs one at a time, using one hand only and put them into the holes in any order until the holes are all filled. The time is stopped in seconds for putting the picks from the container to the board and removal of them one at a time and putting them back to the container. An alternative scoring is the recording of the number of pegs placed in 50 or 100 s. The test only takes 10 min to conduct and is easy to perform. Normative data from able-bodied persons are available, and it has evolved as one of the standard tests for assessment of stroke survivors. However, its validity has not yet been shown in the SCI population.

The Van Lieshout test (VLT) was originally developed to assess basic functional modalities of the arm and hand in individuals with cervical SCI. The short form (VLT-SF) assesses in ten items the positioning and stabilising of the arm, hand opening and closing using the tenodesis effect, grasping and releasing of objects and manipulation of objects using thumb and fingers. Administration time is between 25 and 35 min.

The Spinal Cord Independence Measure version III (SCIM III) measures the ability of patients with SCI to perform everyday tasks according to their value for the patient on a comprehensive rating scale from 0 to 100. SCIM III covers 19 tasks grouped into four subscales: self-care (scored 0–20), respiration and sphincter management (0–40), mobility in room and toilet (0–10) and mobility indoors and outdoors (0–30). The SCIM has the advantage that it can be performed by either face-to-face interview or by phone. The SCIM does not need extra equipment and can be performed relatively quickly in 10–20 min. It is particularly useful as an adjunct measure to ISNCSCI in order to identify the rehabilitation potential of patients.

22.8.1.3 Assessments on Participation

The Canadian Occupational Performance Measure (COPM) is an important assessment allowing a user-centred definition of therapy goals and priorities [29]. The patient's current difficulties in the domains self-care, productivity and leisure activities are determined by in most parts standardised interviews. After the completion of the interview, the patient ranks the priority of each of the items and thereby defines the therapeutic goals for the near future. The COPM interview takes 10–15 min; however, patients often find it hard to focus in their answers and take the opportunity during the interview to tell everything they are unhappy with. It is therefore the duty of the interviewer to guide a patient through the assessment. If

regularly performed the COPM forms an effective tool to define and adapt rehabilitation goals and to enhance the communication between patients and therapists.

The Occupational Therapy Assessment is intended for assessment of the consequences of the neurological impairment on participation and activities of adults [31]. It is based on a four-grade rating scale of different items in eight domains: assistive devices, self-care, autonomy, sensorimotor functions, neurological-cognitive functions, psychosocial interaction and participation in work and leisure activities. It has been validated only in German but is intended to be translated also into English. The assessment takes between 30 and 45 min and can also be performed via phone.

22.8.1.4 Assessments on Assistive Technology

In a client-centred rehabilitation approach, it is often important to obtain information on the user satisfaction with assistive technology. There are some standardised assessments existing to obtain information from end users of assistive devices in a systematic fashion. Among them is the Quebec User Evaluation of Satisfaction with assistive Technology (version 2.0) (QUEST 2.0), consisting of an eight-item device domain and a four-item service domain to measure user satisfaction with a broad range of assistive technology devices [9]. QUEST 2.0 shows excellent validity and takes about 10–15 min to administer either interview based or self-reported.

The Assistive Technology Device Predisposition Assessment (ATD PA) assesses the consumer's subjective satisfaction with current achievements in a variety of functional areas. The consumer characterises aspects of her or his functioning, temperament, lifestyle and views of a particular assistive device [49]. ATD PA has 63 items in two domains. The interview takes about 30 min and excellent reliability and validity has been reported.

Conclusions

The individual human being with high SCI is and will be the focus of all therapeutic efforts aiming at maximisation of her or his autonomy and independence. Over the last decade, a shift towards older patients with more comorbidities and complications occurred, leading to a more time-consuming, complicated and less compliant rehabilitation process. On the other hand, the percentage of patients with incomplete lesions increased over the last 20 years with the need for highly individualised therapy regimes. The shortening of the initial rehabilitation period makes it hard to decide when to move from restorative therapy approaches to compensatory or substitutive therapies.

The diversity of neurological and musculoskeletal conditions of individuals with SCI together with large differences in patients' priorities results in highly personalised treatment regimes. Due to this non-standardised rehabilitation approach, scientific evidence is low for the efficacy of occupational therapies. There is obviously the need for large-scale studies to show the superiority of one therapeutic procedure over the others; however, it will be hardly impossible to implement adequately powered randomised controlled trials (RCTs) to identify the best therapeutic approach and to set up rules for standard rehab procedures.

The available evidence for certain therapeutic procedures such as stretching or splinting is mainly based on a small number of study participants. There is the general risk that the heterogeneity of the study population masks therapeutic effects in subgroups, and one should be very careful not to disqualify therapies from being effective just on the basis of the results of RCTs.

A review of the available literature suggests that training of the upper limb following SCI, including exercise therapy and functional electrical stimulation, leads to improvements in muscle strength, upper-limb function and activities of daily living and finally in quality of life. Further research is needed on the use of new technology, such as cortical neuromodulation therapies (repetitive transcranial stimulation or transcranial direct current stimulation) and robotic devices, in improving upper-limb function (see also Chapter 24). Novel methods such as nerve transfers [50] might open up new possibilities for the restoration of upper-limb function. The outcomes of all these novel interventions need to be studied by carefully designed studies with high trial power and external validity.

Another issue hindering the comparison of study results is the variety of outcome measures used in different trials. Comparison of results across studies would be improved by standardisation of outcome measures. There are initiatives to develop international standards and data sets for upper extremity function in persons with cervical SCI [3]. However, in the framework of studies, these might not be comprehensive enough. The SCIM is often recommended to assess activities of daily living in patients with SCI the relatively new GRASSP might evolve in the future to a standard arm and hand function test; however, it will be hard to implement this assessment in clinical routine due to the time demands. Nevertheless, the routine use of standardised objective tests would allow future meta-analyses of the effectiveness of exercise interventions on upper-limb function from a number of smaller studies.

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Neurorehabilitation: Strategies of Lower Extremities Restoration

23

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Abstract

Treatment of acute spinal cord injury (SCI) comprises two major therapeutic concepts, which aim for either restoration or compensation. Both strategies aim to reach the highest level of quality of life, mainly reflected by independence and participation in social activities. Restoration in this context means to recover sensorimotor function, which has been impaired or abolished by an incomplete spinal cord or cauda equine lesion. Therefore, only in patients with spared sensorimotor axon pathways restorative strategies can be successfully employed. In contrast, compensation means to replace irreversibly lost function through an alternative strategy, e.g., wheelchair mobility will substitute for the mobility achieved through walking. A number of excellent textbooks describe compensatory strategies in SCI rehabilitation in detail. This chapter will focus on therapies to promote recovery of walking function.

In order to choose appropriate rehabilitative treatment strategies, a precise definition of realistic goals to be achieved in each patient is of utmost importance. Respective goals can only be determined once neurological dysfunction and functional deficits are properly assessed. Therefore, effective goal setting approaches and internationally accepted neurological and functional assessment schemes will be described. Accordingly, task specific therapies (e.g., body weight supported treadmill training), supporting therapies (conventional physical therapy targeting muscle strength, balance and trunk stability, functional electrical stimulation) and orthotic devices including wearable exoskeletons will be described.

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23.1 Planning and Goal Setting

The rehabilitation process of spinal cord injury (SCI) patients includes multiple phases and a variety of interventions with the aim to maximize independence and to participate in the social environment. This can be accomplished by means of compensation or restoration. Compensation in this context means that the rehabilitative therapy aims to change movement strategies, which will allow to substitute for the function that has been lost after SCI. For example, wheelchair mobility is the main compensatory strategy to replace lost walking ability in motor complete SCI. In contrast, restorative strategies in the rehabilitative context train incomplete SCI patients to regain lost motor function. As an example, locomotor training – from body-weight-supported treadmill training to unsupported overground walking – can be employed to restore locomotor function after sensorimotor incomplete SCI.

Due to the increasing number of incomplete SCI patients – mainly ASIA Impairment Scale (AIS)-C/AIS-D – a shift in the therapeutic focus has become apparent [1]. Compensatory therapies become more frequently supplemented by approaches to restore lost or improve impaired motor functions. In this chapter we focus on the recovery of standing and walking function. Irrespective of restorative or compensatory rehabilitative strategies, appropriate patient goals should be defined based on the International Classification of Functioning, Disability and Health (ICF). Accordingly, short- and medium-term goals correspond to the level of activity and function, whereas long-term goals reflect the patient's life goals and participation [2]. Short- and medium-term goals can change daily, weekly, or monthly and should be achievable within the time frame of the rehabilitation process. Respective goals should be oriented toward the long-term objectives and at the same time need to be adapted to the current situation during the rehabilitation process. The goals, especially those concerning participation, should be decided by the patient and not by the treatment team. Here, the fact of defining goals does not mean that they must always or can always be achieved. It is more a case of formulating long-term prospects that will probably have to be revised or modified during the treatment.

Clinical Case A female patient with incomplete paraparesis (T8; AIS-C) wants to return back into her apartment, which can only be reached via a few stairs. As a consequence, the restorative concept aims to train getting up from the wheelchair and climbing stairs independently, thus defining short- and medium-term goals. In case climbing stairs through a restorative strategy cannot be achieved, assistive devices for stair climbing will be considered, and relatives will be trained to support the patient in this task.

At the beginning of the inpatient rehabilitation treatment, the multidisciplinary professional team should meet to define the current status of the patient and to establish short- and medium-term goals considering the patient's perspective. To standardize this process, a goal setting scheme should include the neurological, musculoskeletal, nutritional and functional status of the patient (Tables 23.1 and 23.2). For each of these items, the goals and the appropriate rehabilitative approach

Table 23.1 Goal setting: according to the current neurological status, a realistic goal and the appropriate therapeutic intervention can be chosen (goal setting scheme – Heidelberg University Hospital).

Current status	Goal	Therapeutic intervention
☐ Sensory complete ☐ Sensory incomplete ☐ Motor complete ☐ Motor incomplete	☐ Compensation ☐ Sensorimotor restoration	☐ Wheelchair skills ☐ Wheelchair sports ☐ Body-weight-supported treadmill (with/without exoskeleton), overground walking ☐ Functional training upper extremities ☐ Turning, sitting, transfer ☐ Activities of daily living ☐ Functional electrical stimulation ☐ Muscle strengthening – not task specific ☐ Testing/prescription assistive devices ☐ Instruction/training of caregivers ☐ Other PT measures (bench, mat training)

PT physiotherapeutical

Table 23.2 Goal setting: according to the neurological complications, a realistic goal and the appropriate therapeutic intervention can be chosen (goal setting scheme – Heidelberg University Hospital)

Current Status	Goal	Therapeutic intervention
☐ Spasticity, myoclonus ☐ (neuropathic) pain ☐ Autonomic dysreflexia (AD) ☐ Others (sweating)	☐ Reduction of spasticity ☐ Reduction of pain ☐ Reduction of autonomic dysreflexia (AD)	☐ Identification of spasticity, pain, AD trigger ☐ FES, treadmill, tilt table ☐ Other PT interventions (proper positioning, Kinesio tape, lymphatic drainage, massage, TENS) ☐ Antispastic medication ☐ Analgesic medication

PT physiotherapeutical, *FES* functional electrical stimulation, *TENS* transcutaneous electrical stimulation

will be checked. Patient status, goals, and approaches will be reviewed weekly and adjusted if necessary. The focus on restorative versus compensatory strategies is based on the SCI severity and the level of neurological injury according to the International Standards for Neurological Classification of SCI (ISNCSCI). In addition, the patient's age and relevant comorbidities including disease prognosis (e.g., spinal cord compression due to metastatic cancer) will affect the goal setting process [3]. Among other things, increasing age is associated with a lower level of functional outcome despite comparable changes in the neurological status between different age groups [4].

Therapies for individuals with motor complete SCI (AIS-A/AIS-B) mainly focus on compensatory interventions. Restorative strategies have been shown to elicit neurological improvement such as improved electromyographic (EMG) activity in paretic muscles. However, it is not possible to achieve clinically meaningful functional improvement in severely affected SCI patients with such interventions [5]. In motor incomplete SCI patients (AIS-C/AIS-D), we aim for restoration, unless an

unfavorable underlying disease prognosis, serious concomitant disease condition(s), or advanced age contradicts. Since the outcome cannot be exactly foreseen in incomplete SCI patients due to a considerable variability in respect to functional and neurological recovery, it is advised to add compensatory rehab strategies to the overall program. Since the length of stay in SCI centers has been dramatically cut down over the years, there is no room for starting compensatory approaches once restorative treatments have failed. The prime goal should always be to discharge an independent patient – be it through restoration of walking and standing or through independent wheelchair mobility. Vice versa, if a rather complete SCI individual gains sensorimotor function over time, restorative concepts will be added to the compensation-centered rehab approach. Of course, therapists should be aware of the fact that patients with prime focus on compensatory elements sometimes do not understand and support such a concept. They expect that functions can be restored irrespective of injury severity, especially when they extrapolate from more incomplete SCI patients, who are challenged with body-weight-supported treadmill training instead of training of wheelchair skills. Such conflicts require careful information of the patient's conditions and explanations, why rehab goals are important in order to obtain independence in everyday life. Nevertheless, despite appropriate goal setting, one of the main difficulties of reintegration reported by patients with SCI during the first year following discharge from hospital relate to mobility aspects such as transfer problems [6].

Overall, patient education in respect to the nature of the disease, shared decision-making related to treatment goals, and adaptation of the rehab strategy based on the extent of neurological recovery represent key aspects for a successful rehabilitation process [7, 8].

23.2 Assessments

A goal-oriented rehabilitation treatment plan requires to obtain objective information about the current patient status. This involves evaluating the physical and functional status as well as recording aspects, which may affect the rehabilitation process, e.g., presence and severity of pain, preexisting medical and functional conditions, and current medication. Respective assessments will facilitate the initial goal setting process and over time serve as a basis to adjust therapeutic goals and related interventions accordingly.

The relevant assessments can be divided into (1) testing of the function and structure of the body (e.g., examination of sensory and motor function, manual muscle testing, testing the range of motion, and movement control examinations) and (2) functional outcome measures (e.g., Walking Index for Spinal Cord Injury, Timed Up and Go, etc.).

23.2.1 Neurological Function

The ISNCSCI is developed and published by the American Spinal Injury Association (ASIA), currently on its sixth edition. It is the worldwide accepted tool to determine

motor and sensory impairments in SCI individuals in standardized fashion. The examination contains sensory and motor components to determine the neurological level and to classify the severity of the injury according to the AIS. The neurological level of injury (NLI) refers to the most caudal segments with intact sensory and motor function. The severity of the injury is graded in five steps ranging from A (complete SCI) to E (normal sensory and motor function) [9–11]:

A	Complete. No sensory or motor function is preserved in the sacral segments S4–S5
B	Sensory incomplete. Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4–S5, and no motor function is preserved more than three levels below the motor level on either side of the body
C	Motor incomplete. Motor function is preserved below the neurological level, and more than half of key muscle functions below the single neurological level of injury have a muscle grade less than 3
D	Motor incomplete. Motor function is preserved below the neurological level, and at least half of key muscle functions below the NLI have a muscle grade of 3 or more
E	Normal. If sensation and motor function as tested with the ISNCSCI are graded as normal in all segments

The sensory examination requires the testing of a key point in each of the 28 dermatomes (from C2–S4–5) bilaterally for light touch and pinprick. All sensations are scored with three points: 0 = sensation is absent; 1 = sensation is impaired or partial appreciation, including hyperesthesia; and 2 = sensation is normal. Besides deep anal pressure is examined and should be graded as being present or absent.

Within the motor examination, ten key muscles of the myotomes C5–T1 (*C5, elbow flexors*; *C6, wrist extensors*; *C7, elbow extensors*; *C8, finger flexors*; *T1, small finger abductors*) and L2–S1 (*L2, hip flexors*; *L3*, *knee extensors*; *L4*, *ankle dorsiflexors*; *L5*, *long toe extensors*; *S1*, *ankle plantar flexors*) are assessed on both sides with manual muscle testing. Furthermore, the voluntary anal contraction is assessed and scored as absent or present [9–11].

23.2.1.1 Manual Muscle Testing

Manual muscle testing (MMT) according to Janda is based on a subjective assessment, in spite of its well-defined scale of strength levels. Furthermore, the test only allows the state of the muscles at a specific instant to be evaluated and does not allow the assessment of muscle fatigue. Yet muscle testing according to Janda is a firmly established part of routine clinical practice and an important component of physical examinations. The approach identifies six fundamental stages (Table 23.3) [12]:

In the examination concerning the lower extremities, in addition to the key muscles of the myotomes L2–S1 of the ISNCSCI examination (as mentioned above), the hip extensors, the hip abductors and adductor, and the knee flexors should be examined.

23.2.1.2 Range of Motion

The range of motion (ROM) of individual joints and the spine has a considerable influence on the patient's function and the level of independence after SCI. For example, limited spine movement following extensive spinal fusion surgery can

Table 23.3 Manual muscle testing

Level of strength	Description
5	Corresponds to a muscle with normal strength, which is able to negotiate intensive resistance within the full range of movement. Important: this does not mean that the muscle is without pathological findings when performing all functions (e.g., fatigue)
4	The muscle tested can perform a movement to the full range and negotiate medium resistance (corresponds to approx. 75 % of normal muscle strength)
3	The muscle tested can perform a movement to the full range against gravity. Additional resistance cannot be negotiated (corresponds to approx. 50 % of normal muscle strength)
2	The muscle tested can perform a movement to the full range but only when gravity is eliminated since the tested extremity cannot hold its own weight (corresponds to approx. 25 % of normal muscle strength)
1	The muscle tested can be contracted, but the tested extremity cannot be moved (corresponds to approx. 10 % of normal muscle strength)
0	No signs of arbitrary muscle contraction

be a cause for patient's inability to carry out intermittent catheterization independently. The neutral zero method is used to describe the maximum possible passive and active range of motion of a joint in all possible planes of movement based on a standard initial position. First, the angle of maximum movement away from the body is given, then the 0-position (zero), and finally the angle of maximum movement toward the body. If motion is limited, the zero (0-position) will not appear in the middle but on the side upon which there is a deficit [13]. Taking the upper ankle joint as an example, unlimited range of motion would mean plantar flexion/dorsal extension: 50°/0/30°. In the case of *pes equinus*, the following result may be obtained, depending on the range of motion: 50/20°/0°. In this case, the neutral position cannot be achieved, and there remains a residual flexion of 30° between 20° and 50° plantar flexion. The lack of a neutral position in the upper ankle joint may prohibit a proper sitting position in the wheelchair causing secondary strain to the ischii. Worst case, sitting in the wheelchair may become impossible.

23.2.1.3 Spasticity Measure

The *Modified Ashworth Scale* is frequently used for grading spasticity in routine clinical practice. It can be easily performed and does not require any equipment. The velocity-dependent response of muscles to passive stretching is rated in a six-point nominal scale [14]: 0 = no increase in muscle tone; 1 = slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion when the affected part(s) is moved in flexion or extension; 1+ = slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the ROM; 2 = more marked increase in muscle tone through most of the ROM, but affected part(s) easily moved; 3 = considerable increase in muscle tone, passive movement difficult; and 4 = affected part(s) rigid in flexion or extension.

Of note, the Ashworth Scale represents a subjective assessment and only checks single-joint resistance to passive ROM at a specific point in time. The interaction of muscle chains, the spasm frequency, or possible spasticity triggers are not examined. Even the impact of spasticity on function cannot be assessed.

The *Penn Spasm Frequency Scale* (*PSFS*) represents a patient-reported outcome measure. However, its reliability has yet to be confirmed. The patient completes a self-assessment questionnaire reporting spasm frequency (*0 = no spasms*, *1 = spasms induced only by stimulation*, *2 = infrequent spontaneous spasms occurring less than once per hour*, *3 = spontaneous spasms occurring more than once per hour*, *4 = spontaneous spasms occurring more than ten times per hour*) and intensity (*1 = mild*, *2 = moderate*, *3 = severe*) [15]. More details on spasticity measures can be found in chapter 13).

23.2.2 Functional Outcome Measures

23.2.2.1 Spinal Cord Independence Measure

The Spinal Cord Independence Measure, version III (SCIM III), specifically designed for individuals with SCI, is a comprehensive disability scale [16, 17]. The assessment reflects aspects of self-care management, medical conditions, and mobility. The tool is grouped into three areas of function and takes approx. 30 min to complete, ideally by observing the patient (Table 23.4). The test does not require any particular equipment and can be incorporated into clinical routine.

The first section involves the item of self-care – feeding, bathing, dressing, and grooming – with a total score of 20 points. The second section refers to activities of respiration, bladder sphincter management, and bowel sphincter management and collects a maximum of 40 points. The third section reflects all aspects of mobility with 40 points total to be achieved. Thus, a maximum of 100 points can be reached from all sub-items, whereas increasing number of points reflects improved independence [18].

23.2.2.2 Spinal Cord Injury Functional Ambulation Inventory (SCI-FAI)

The gait assessment is SCI specific and easy to assess and evaluates three components of walking: gait pattern (Table 23.5) with a maximum of 20 points, the use of assistive devices (e.g., cane, walker, orthosis) with a maximum of 14 points, and walking modalities such as speed, frequency, and distance with five possible points. Higher scores denote a higher level of walking ability, although the subscores should not be combined to make an overall score. The measurement is a combination of observation and the patient's self-report [18, 19].

23.2.2.3 Walking Index for Spinal Cord Injury

The Walking Index for Spinal Cord Injury (WISCI) is a functional scale for clinical use and for research to evaluate improvements in ambulation. In the second version (WISCI II) with two additional levels, the walking capability is rated from 0 to 20 based on the individual's dependence on assistive devices, braces,

Table 23.4 Main parts of SCIM III

Self-care
Feeding: cutting, opening containers, pouring, bringing food to mouth, holding cup with fluid (0–3 points)
Bathing: soaping, washing, drying body and head, manipulating water tap: upper body (0–3 points), lower body (0–3 points)
Dressing: clothes, shoes, permanent orthoses: dressing, wearing, undressing: upper body (0–4 points), lower body (0–4 points)
Grooming: washing hands and face, brushing teeth, combing hair, shaving, applying makeup (0–3 points)
Respiration and sphincter management
Sphincter management – bladder (0–15 points)
Sphincter management – bowel (0–10 points)
Use of toilet: perineal hygiene, adjustment of clothes before/after, use of napkins or diapers (0–5 points)
Respiration (0–10 points)
Mobility (*room and toilet*)/*mobility* (*indoors and outdoors*, *on even surface*)
Mobility in bed and action to prevent pressure sores (0–6 points)
Transfers: *bed to wheelchair*: locking wheelchair, lifting footrests, removing and adjusting arm rests, transferring, lifting feet (0–2 points)
Transfers: *wheelchair to toilet to tub*: if uses toilet wheelchair: transfers to and from; if uses regular wheelchair: locking wheelchair, lifting footrests, removing and adjusting armrests, transferring, lifting feet (0–2 points)
Mobility: indoors (0–8 points), moderate distances (10–100 m) (0–8 points), outdoors (more than 100 m) (0–8 points)
Stair management (0–3 points)
Transfers: *wheelchair to car*, approaching car, locking wheelchair, removing arm- and footrests, transferring to and from car, bringing wheelchair into and out of car (0–2 points)
Transfers: *ground* to *wheelchair* (0–1 points)

Adapted from Catz and Itzkovich [17]

and personal assistance. The examiner observes the patient, who walks 10 m, and rates the level, which is considered to be safe. Level 0 describes that the client is unable to stand and/or participate in assisted walking. At level 1 the patient ambulates in parallel bars, with braces and physical assistance of two persons, less than 10 m. At the highest level 20, the patient ambulates with no devices, no braces, and no physical assistance over a distance of at least 10 m [18, 20]. The use of the WISCI is limited in assessing individuals with only minor walking impairment due to a ceiling effect. Walking endurance is not reflected in this score [21].

23.2.2.4 6-Minute Walk Test

The 6-minute walk test (6 MWT) measures the distance a patient can walk on a flat surface as quickly as possible in 6 min. The patient may stop and rest (but not sit) during the test, and the use of auxiliary equipment is also permitted. Along with the ability to walk, endurance and cardiopulmonary capacity are also evaluated, among other things. The test was originally designed for patients with respiratory impairments. In

Table 23.5 Observational gait analysis part of the SCI-FAI

Parameter	Description
Weight shift	Weight shift to stance limb or weight shift absent or only onto assistive device
Step width	Swing foot clears stance foot on limb advancement or stance foot obstructs swing foot on limb advancement
	Final foot placement does not obstruct swing limb or final foot placement obstructs swing limb
Step rhythm (relative time needed to advance swing limb)	At heel strike of stance limb, the swing limb: begins to advance in <1 s or *r*equires 1–3 s to begin advancing *or* requires >3 s to begin advancing
Step height	Toe clears floor throughout swing phase or toe drags at initiation of swing phase only or toe drags throughout swing phase
Foot contact	Heel contacts floor before forefoot or forefoot or foot flat first contact with floor
Step length	Swing heel placed forward of stance toe or swing toe placed forward of stance toe or swing toe placed rearward of stance toe

Adopted from Field-Fote et al. [19]

the case of incomplete SCI patients, the 6 MWT is particularly suitable for individuals with minor impairments, in order to record further improvement [18, 22, 23].

23.2.2.5 Timed Up and Go

The Timed Up and Go (TUG) is a timed walking test, which was originally developed to assess the sense of balance in elderly individuals and the resulting danger of falling. The TUG records the time (in seconds) that the patient needs to rise from a chair, to walk three meters, to turn around when they get to the 3-m line, and to walk back and sit back down on the chair [24]. If it takes the patient more than 30 s to accomplish the task, they will normally require help for transfers and going up stairs, and they are not able to go outside alone. Use of auxiliary equipment is permitted. The test is easy to carry out and can be used to assess walking ability, even in SCI patients, although no standard value has been established for the SCI population at this time [18].

23.2.2.6 10-Meter Walk

For the 10-meter walk test (10 MWT), the patient must be able to walk at least 14 m as this is the total distance to be covered in this test. It measures the time in seconds that the patient needs to walk 10 m, from meter 2 to meter 12 ("flying start"). Assistive devices may be used [25]. However, the use of auxiliary devices is not taken into account when scoring, and no statement can be made about endurance due to the walking distance only being 10 m. The test can be used in a clinical context and to evaluate walking ability in individuals with SCI in clinical studies [18, 24].

23.2.2.7 Berg Balance Scale

Initially developed for elderly persons, the Berg Balance Scale (BBS) is now also used for stroke and SCI patients as well as those suffering from multiple sclerosis. It comprises a total of 14 items, which are each assessed on a 5-point scale. The

overall number of points ranges from 0 points (severely impaired balance) to 56 points (excellent balance). The categories are as follows:

1. Sitting to standing
2. Standing unsupported
3. Sitting with back unsupported but feet supported on floor
4. Standing to sitting
5. Transfers from an armless chair to a chair with arms
6. Standing unsupported with eyes closed
7. Standing unsupported with feet together
8. Reaching forward with outstretched arms
9. Picking up an object from the floor
10. Turning to look behind over left and right shoulders
11. Turning 360°
12. Placing alternate feet on step or stool while standing unsupported
13. Standing unsupported one foot in front
14. Standing on one leg

The test can be used in all phases, but only for patients who possess a certain level of standing and walking ability [18, 26].

23.3 Therapeutic Strategies for Lower Extremity Rehabilitation

23.3.1 Compensation Toward Functional Independence

This chapter focuses on strategies to promote recovery of walking function. For compensatory strategies, it is referred to respective textbooks. The main goal of rehabilitation is to achieve the maximum level of independence, which can be achieved to a varying extent depending on the lesion severity, level of injury, and concomitant comorbidities. It is acknowledged that for individuals with severe/high-level SCI, compensatory strategies and assistive technology represent the only alternative to regain functional independence.

If it is not possible to restore the standing and walking function sufficiently for everyday life or if this is not yet foreseeable within the scope of the initial treatment, the rehabilitation team has to encourage the patient to work toward functional independence. Patients with severe motor impairments, who converted from walking at discharge to the wheelchair within 1 year after injury, experienced poor quality-of-life factors with high levels of depression and pain scores [27].

Individual rehabilitation plans have to be constantly adapted to the current level of therapy and supplemented by compensatory elements. It is essential to practice also wheelchair mobility, transfer skills, and activities of daily living and adapt the necessary devices. Just one example which is choosing the appropriate wheelchair is an individual decision and depends on a great many factors. Using a mechanical

wheelchair requires sufficient functioning of the upper extremities, the trunk muscles, and corresponding cardiopulmonary capacity. If these conditions are not met, use of an electrical device/electrical wheelchair must be examined. Further criteria include, among other things, the sitting position, primary use (indoor, outdoor, for sport), and the patient's demands on the wheelchair. For detailed descriptions and instructions of compensatory strategies/skills, see, for example, Somers and Harvey [28, 29].

23.3.2 Restoration of Locomotor Function

The main goal in lower extremity functional restoration is recovery of – ideally unaided – walking function. Depending on the degree of spared functions, the therapy can also address the ability to get up and stand to facilitate movement transition, e.g., during transfer or to make use of remaining upper extremity function.

Walking is a complex process, which requires adequate voluntary motor function, sufficient coordination of leg movements, and – often neglected – appropriate sensory feedback, in particular proprioceptive feedback. These basic prerequisites allow to shift the body weight on one side during the standing phase, achieve an upright posture and stability of the trunk, maintain the balance, and adapt to the environment as needed. For successful restoration of walking function, sufficient joint mobility in the lower extremities represents an important prerequisite [30]. In the course of locomotor training, auxiliary equipment including support (compensation) through the intact upper extremities might be necessary. Therefore, this chapter will not only focus on the task-specific aspects of locomotor training but in addition discuss supporting elements, which are key for restoration of locomotor function such as trunk stability, endurance, and the implementation of supportive devices (e.g., orthoses).

23.3.3 Task-Specific Locomotor Training

In order to learn or relearn defined motor skills, the principles of motor learning have to be employed. These principles rely on practice (number of repetitions) and augmented feedback about performance. Moreover, training needs to be task specific – if you want to walk, you have to walk. An optimal rehab program aiming for recovery of walking function should not only rely on task-specific locomotor training. Supporting measures, e.g., trunk stability or muscle training (see below) have to be employed to improve the efficacy of task-specific training. Unfortunately, evidence in respect to the optimal timing/dose of task-specific training, the most efficient feedback approach or the ideal balance between task-specific and unspecific training is scarce.

The most important principles for locomotor training are increasing the ability of the lower extremities to take on weight and reducing the amount of weight taken on by the upper extremities, augmenting sensory input, and strengthening movement

sequences as well as reducing compensatory strategies (e.g., assistive equipment, therapist support) [3, 31]. In the early phase after spinal cord injury, in particular in cases of more severe motor impairment, automated locomotor therapy represents an important therapy option. Despite severe sensorimotor deficits, task-specific training can be employed at a rather high repetition rate without exhausting the therapist too much [3, 32]. However, the limited variability and perturbation options due to the restrictive nature of robotic assistance represent the downside of such a therapy [31]. Until now none of the proposed task-specific locomotor training concepts have been clearly shown to be superior in patients with incomplete SCI [33]. The choice of the machines to assist training depends on the extent of sensorimotor deficits in the lower extremities and trunk as well as the cardiopulmonary capacity.

In patients with a high level of injury, severe sensorimotor deficits and orthostatic dysregulation are treated first on a tilt table, which allows stepping movements (see below). Once orthostatic dysregulation has ceased, body-weight-supported treadmill training with exoskeletal support will be tested. In case only minor leg assist is required, stepping movements can be induced without external support, and body weight can be taken over at least partially by the patient; treadmill training with body-weight support, however without exoskeletal support of the lower extremities, will continue. Subsequently treadmill training will be mixed with overground locomotor training and as soon as possible replaced by overground training activities (Fig. 23.1).

During supported treadmill training, requirements for overground mobility should already be addressed by the therapist. Ideally, at the end of each treadmill session, the progress in locomotor function should be practiced without assistive devices. Depending on the degree of neurological recovery, getting up from height-adjustable benches, weight shift while standing, taking one step forward and to the side, stepping on the spot, or overground walking can be exercised [34].

23.3.3.1 Locomotor Training Devices

Tilt Table with Stepping Device

The tilt table with stepping function (ERIGO®) is based on a traditional tilt table allowing stepping with a physiological load pattern in combination with an adjustable tilt and stepping frequency. The patient is secured through a harness with a chest and shoulder fixation (Fig. 23.2). Each thigh is fastened by a cuff and each foot is fixed on a footplate by two straps. The upper body part of the tilt table can be continuously tilted from the supine position up to an angle of 80°.

To realize a physiologically gait-related loading of the foot, a special spring damper was integrated in the footplate: Load is applied to the foot sole during the stance phase (hip and knee extension) due to clamping of a spring beneath the plate. In case of hip and knee flexion, the spring is released from the plate and load reduction is generated. The overall load on the foot increases with the degree of tilting since the patient's body weight becomes more and more exposed to gravity pushing against the spring-damped footplate [35].

Stepping movement requires loading of the legs to induce a patterned leg muscle activation in healthy subjects and individuals with spinal cord injury. The

Fig. 23.1 Practice of walking function in an incomplete SCI patient. (**a**) Body-weight-supported treadmill training with exoskeletal support (Lokomat®). (**b**) Overground walking on parallel bars. (**c**) Overground walking on parallel bars with visual feedback (mirror). (**d**) Initiation of overground walking by getting up from the bench to stand. (**e**) Overground walking with a walker on a homogenous surface

appearance of a locomotor pattern depends on afferent input detected by "load receptors" in combination with hip joint position-related proprioceptive input [36, 37].

The efficacy of ERIGO® training has only been demonstrated in ameliorating orthostatic dysregulation [38]. Heart rate and blood pressure increased over time superior to effects seen with a tilt table without stepping function. It can be assumed that early training with the ERIGO® improves locomotor function. However, this has yet to be determined. Nevertheless the ERIGO® is employed to practice gait training in patients with poor sensorimotor function at a very early stage of rehabilitation. The concept behind this strategy is to deliver weight bearing to the legs as early as possible in order to avoid maladaptive changes on one hand and to prepare an optimal setting for subsequent more task-specific locomotor training [3].

Fig. 23.2 Tilt table with stepping function

Manually Assisted Body-Weight-Supported Treadmill Training

Treadmill training with body-weight support has become an important part of gait rehabilitation for patients suffering from incomplete SCI. In addition to an increase in walking speed and walking distance as well as a reduction in the need to use assistive devices, locomotor training has also been correlated with an increase in bone and muscle mass along with positive cardiovascular effects [5, 31, 39–43]. Comparing standard physical therapy alone with a combination of body-weight-supported treadmill training and standard physical therapy in patients with acute incomplete SCI indicated that patients receiving the combinatory treatment gained independence from assistive devices/walking aids more rapidly and achieved a higher walking speed than patients with standard physical therapy [44].

Treadmill training is ideally suited to implement the abovementioned principles of locomotor training. Body-weight support can be adjusted to the maximum weight transfer possible to both legs (it should still be possible to straighten knee and hip joints). As a consequence, the amount of weight taken by the upper extremities [3, 45–47] can be reduced. In addition, walking speed can be adjusted close to the average walking speed (0.75 – 1.25 m/s) [3, 40]. Treadmill training allows almost physiological joint movements of the hip, knee, and ankle joints, with particular emphasis on the hip joints [3, 40, 46] including an upright positioning of the trunk [3, 40]. Depending on injury severity, 1–2 therapists have to support coordinated leg movement during swing and stance. Therapy goals have to be reevaluated for each therapy session and respective variables of the walking device have to be adjusted

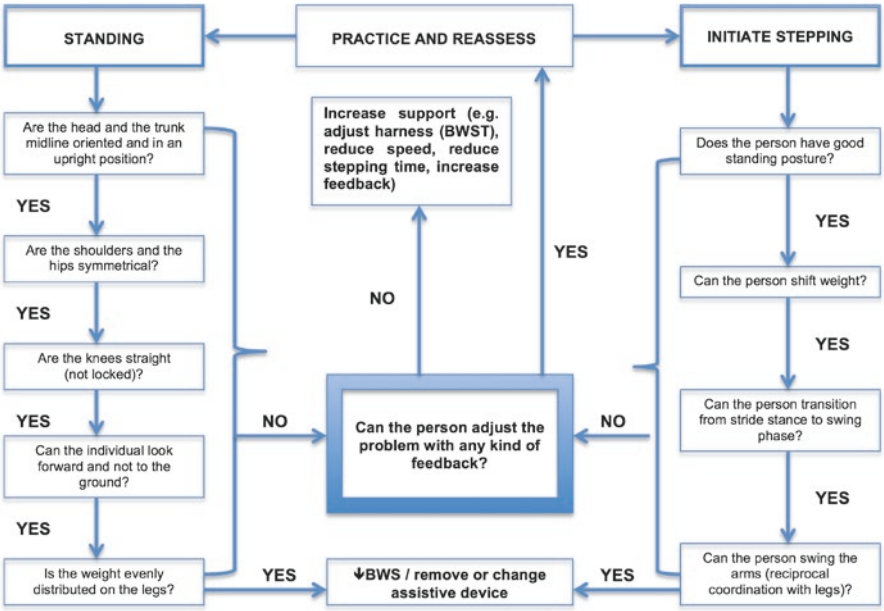

Fig. 23.3 Decision-making algorithm for standing and step initiation progression (Adapted with permission of the American Physical Therapy Association. ©2005 American Physical Therapy Association [48]). *BWST* body-weight-supported treadmill, *BWS* body-weight support

accordingly. Objectives can be to increase walking speed, to reduce body-weight support, to reduce the amount of manual support, or to prolong the training sessions (Fig. 23.3). In the case of reduced proprioception, external feedback via auditory feedback (e.g., therapist) or visual feedback (mirror, technical systems capable to detect gait kinematics) can help to restore a more physiological gait pattern. Instrumented kinematic real-time feedback therapy in individuals with incomplete SCI has been shown to normalize the gait [49].

Robotic-Assisted Body-Weight-Supported Treadmill Training

The main objectives to develop a robotic-assisted body-weight-supported treadmill were to reduce the workload of therapists to position the legs and stabilize the trunk while walking on the treadmill, to generate reproducible gait pattern and as a consequence to intensify gait training with a high number of repetitions. In electromechanical devices for automated-assistive walking training machines, end-effector devices can be distinguished from exoskeleton devices. The Lower Extremity Powered Exoskeleton (LOPES®) [50], the Active Leg Exoskeleton (ALEX®) [51], and the Lokomat® represent exoskeleton-based robotic-assisted body-weight-supported treadmills. Examples for end-effector-based devices are the G-EO-System, the LokoHelp, the Haptic Walker, and the Gait Trainer GT1 [52].

Exoskeleton Based Robotic-Assisted Body-Weight-Supported Treadmill Training

The Lokomat (Fig. 23.4) consists of a robotic gait orthosis, a weight support system, and a treadmill. The gait orthosis primarily consists of a hip and knee orthosis which can be readjusted and adapted to each individual patient. Active actuators are installed in the knee and hip joints for the swing phase. The ankle joint movement is supported by a passive foot lifter. In order to achieve a physiological gait, the powered orthosis is controlled by a computer. Here, the actuators for the hip and knee joint movement follow a physiological specification and provide a reproducible gait pattern. This was determined prior to the administration in patients by testing the Lokomat® on healthy subjects. The devices are equipped with a feedback system for self-control of therapy. Once the patient has been positioned in the Lokomat®, only one therapist is required to perform the therapy, to adjust the parameters (speed, weight support, hip and knee position), and – very important – to give instructions. To ensure the patient's safety, it is recommended that two therapists safely position the patient in the Lokomat® [3, 32, 53]. The Lokomat® has been shown to increase the gait velocity, endurance, and walking distance [54]. In respect to gait quality, the Lokomat® is comparable to manually assisted treadmill training [55–58]. However, the Lokomat® requires less therapists and produces a more reproducible gait pattern.

End-Effector Based Gait Training

This concept is based on two mechanically driven footplates, whose trajectories simulate stance and swing phases during gait training. As a consequence, the

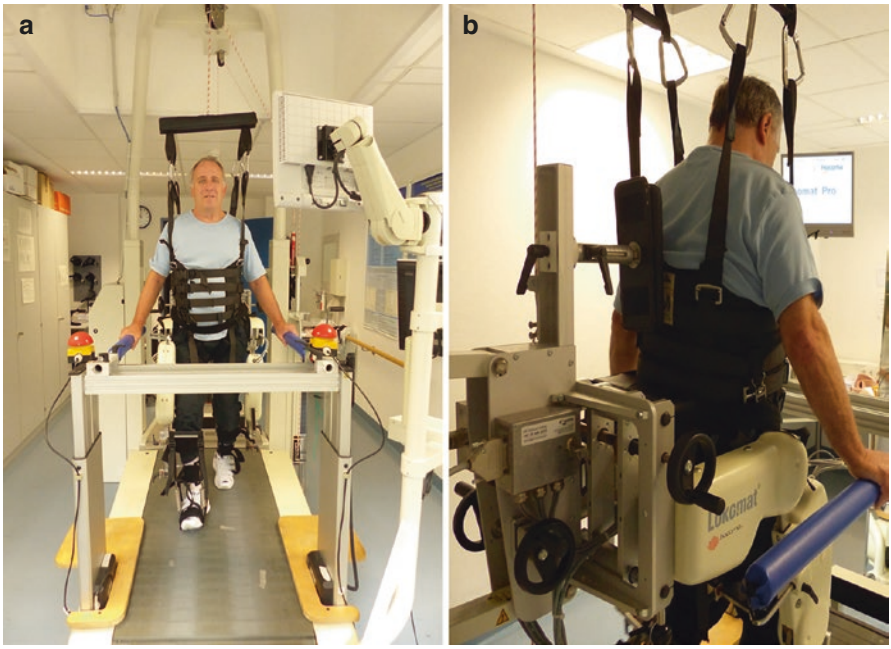

Fig. 23.4 (**a**, **b**) Robotic-assisted body-weight-supported treadmill training with the Lokomat®

machine moves the feet (end effector). The more proximal joints (knee, hip) follow this movement (e.g., G-EO-System, LokoHelp, Haptic Walker, Gait Trainer GT1 [52]). In a multicenter study with 155 acute non-ambulating stroke patients (DEGAS study), end-effector-based gait training in combination with physical therapy has been shown to be superior to physical therapy alone [59]. More advanced machines such as the "Haptic Walker" consist of programmable footplates to simulate a variety of overground walking conditions (stairs, other obstacles) and to introduce perturbation (sudden slipping) [60]. An evaluation of 18 studies (11 trials used an exoskeleton device, 7 trials used an end-effector device) on gait training in stroke patients showed a higher rate of independent walking after training with the end-effector device [52].

A direct comparison of the Lokomat® and the Gait Trainer GT1 in motor incomplete acute SCI patients (predominantly AIS-D) revealed similar improvements in all outcome categories (Lower Extremity Motor Score, Walking Index for Spinal Cord Injury II scale, 10-m walk test). In the reported study, both systems seem to be an adequate tool to improve walking functions in incomplete SCI patients [61]. However, in SCI patients with severe motor impairments in the lower extremities, proximal and distal joints need substantial support, which cannot be provided by end-effector devices. Here, only exoskeleton-based devices represent a feasible treatment option.

MoreGait

The abovementioned devices require trained therapists as well as sufficient space and infrastructure. Due to the high costs, only inpatient rehab facilities or large outpatient institutions can effectively run such a device. However, even in such institutions, unstable patients in the very early rehabilitation phase or patients with multiresistant germs frequently cannot be introduced into respective devices. Moreover, shortening of inpatient stays by health-care providers limits the use of these devices. To address these aspects, a specific locomotor training device – so-called Motorized orthosis for home rehabilitation of Gait (MoreGait) – was developed at Heidelberg University Hospital (Fig. 23.5). The MoreGait consists of a seat with inclined backrest for a semi-reclined position, two active powered

Fig. 23.5 MoreGait

exoskeletons (knee and ankle joints), and a footrest ("stimulative shoe") to allow physiological stimuli to be applied to the foot. Thanks to the semi-reclined position, weight is not applied to the foot due to the patient's body weight but via a mechano-stimulation unit. A movement comparable to walking can be carried out using the training device, whereby a physiological rolling movement of the foot is simulated. A feedback function is integrated in the device to allow control of the therapy and to supply the patient with feedback in respect to his/her training activity. A folding base allows the device to be transported. The therapeutic concept has been evaluated within the scope of a pilot study on chronic motor incomplete SCI participants in an outpatient setting. The results indicated that MoreGait therapy is effective in the home environment. After conclusion of an 8-week training period, a significant improvement was observed in walking velocity along with an increase in endurance [62, 63]. Initially developed for the use at home, the MoreGait device can due to its mobility easily be applied to patients colonized with multiresistant germs.

23.3.3.2 Locomotor Training Overground With/Without Body-Weight Support

Overground walking is the actual objective of the entire locomotor training process. Device-supported therapies only serve to prepare for this objective. Although device-supported therapies are task specific, they are different to overground walking in respect to gait characteristics and muscle activity. Treadmill training represents an effective restorative/rehabilitative treatment option in particular in acute phase following SCI and in cases with severe sensorimotor impairment. As pointed out exercises can be repeated at higher frequency and speed [64]. However, treadmill training cannot replace task-specific overground locomotor training, since it does not allow to manage unexpected obstacles or varying surface conditions [65].

As a first step toward overground locomotion, walking along parallel bars can be trained. In cases with higher sensorimotor deficits, in particular in the pelvic and hip regions, the patient can be instructed to take side steps while his/her hands reach for a parallel bar or an elevated bench for support.

Once the patient can walk overground for the same duration and level of intensity as on the treadmill, walking-related outcome assessments show that device-supported training is no longer advantageous to overground training [43, 66–68]. After each device-supported therapy session, the patient's ability to stand and walk should be checked, and if applicable, overground gait training should be introduced/expanded. In case specific aspects of the gait pattern are not sufficient to allow overground walking, trunk control, involvement of arms, and joint positions should be separately addressed in subsequent – not necessarily task specific – sessions. Overall, device-based treadmill training should be employed as much as necessary and as little as possible, once overground training is feasible (Fig. 23.6).

Subsequent steps during overground training are to reduce assistive equipment (e.g. crutches, walkers, splints) and therapist support. In addition, walking over different terrain and a variety of distractions can be introduced. Five different categories for overground walking have been defined [69]: 1) walking balance (e.g. walking on different surfaces/in different directions), 2) skilled walking tasks

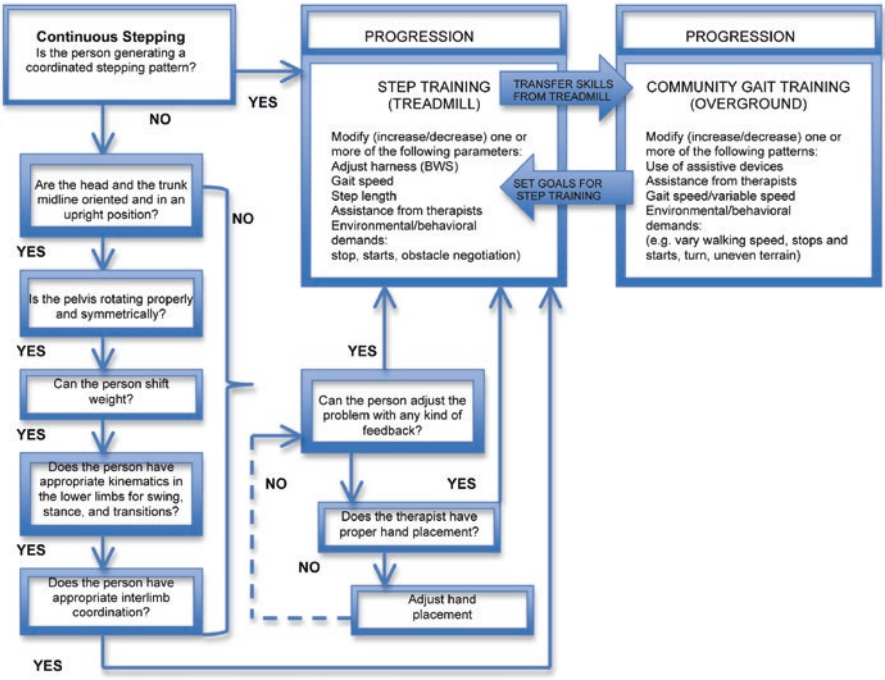

Fig. 23.6 Decision-making algorithm for continuous stepping progression (Adapted with permission of the American Physical Therapy Association. ©2005 American Physical Therapy Association [48]. *BWS* body-weight support)

(e.g. negotiating obstacles, stairs, crowded environments, doors), 3) walking with secondary task (e.g. walking and looking/talking/carrying an object), 4) endurance (e.g. walking over longer distances indoors/outdoors), and 5) speed (e.g. walking short distances at fast pace). Training should also involve walking backwards and practising falling and getting up again.

Overground training can be combined with body-weight support as in the LiteGait system (Mobility Research Inc., Tempe, USA). The mobile training device, which consists of a weight-bearing strap system attached to two overhead supports, can be used over a treadmill and overground. The advantages of this system are its flexibility and its moderate price. Its disadvantages are the number of therapists required to position the patient's legs and correct the trunk. Due to the weight of the device, it also has to be moved by more than one therapist. The wheels attached to the frame allow training only on even ground without obstacles [70].

The so-called Zero G system (Aretech, Ashburn, Virginia 20147, USA) provides also body-weight support while walking overground. The harness is attached to a ceiling track, which can be equipped with a static or a dynamic body-weight support system. The latter guarantees constant weight support and the possibility to change positions. Besides the harness no therapy device surrounds the patient. The therapist has almost unrestricted access to the patient and can provide assistance as needed.

Individuals can walk on different ground surfaces and challenged in varying body positions, e.g., sitting freely on uneven ground. Moreover, assistive devices such as crutches or a walker can be tested while patient is suspended/secured [70]. The fixed position of the ceiling tracks restricts the spatial flexibility of this device. Published clinical studies in SCI or stroke are still pending.

Overall, one should keep in mind that all of the abovementioned assistive devices cannot replace, only assist experienced and skilled therapists. None of them work like a washing machine, where you throw in dirty clothes and receive clean clothes after so many automated washing cycles.

23.3.4 Supporting Therapies

23.3.4.1 Electrical Stimulation

Functional electrical stimulation (FES) is a technique that uses electrical impulses to generate muscle contractions and body movements artificially in individuals with paralysis due to lesions of the central nervous system (upper motoneuron lesion). However, SCI can affect both upper and lower motoneurons. Therefore, electrical stimulation (ES) for each lesion type will be described separately. According to the official definition, we will refer to FES in the context of upper motoneuron lesion and ES in the context of lower motoneuron lesion.

Functional Electrical Stimulation in Upper Motoneuron Type Paresis

FES treatment in lower extremities aims to reduce muscle tone/spasticity [71–73], avoid muscle atrophy, promote muscle strengthening [74, 75], and increase muscle endurance [76, 77]. Moreover, FES-induced muscle contraction/movement in paretic muscles can augment voluntary movement through mechanisms such as embodiment. Furthermore FES can substitute lost central control of paralyzed muscles, e.g., FES-based neuroprosthesis for the correction of drop foot [78]. Positive side effects have been reported such as improvement of bone density [75], cardiovascular strengthening [77], and prevention of decubitus [79].

Paretic/plegic muscles can be activated via FES of corresponding motor nerves. The pulse width used is roughly in the range of 100–500 μs. Stimulation parameters such as frequency, electrode positions, and duration of treatment are selected individually related to the degree of spasticity and fatigue during treatment. Spasticity can be reduced by FES. So far, transcutaneous FES represents the only proven non-pharmacological option to treat spasticity in SCI.

In early FES treatment, spasticity increases during a phase of muscle strengthening. It persists during this training phase, but decreases once a steady force level is observed. This means that the muscle force has reached a plateau. Sometimes spasticity decreases immediately; in other cases, it takes months [71]. In few instances high-frequency FES treatment has to be terminated due to unwanted increase in muscle tone.

Lower stimulation frequencies of 2–6 Hz are adequate to make patients familiar with the stimulation procedure, because single muscle twitches are easily palpable and visible. This trains endurance and prepares the muscle carefully for

strengthening with 16–20 Hz, sometimes up to 35 Hz. A further increase of frequency and intensity can provoke spasticity. Therefore, frequency and intensity need to be adapted carefully according to the training status of the muscles [73].

Muscle strengthening starts at 10–16 Hz, generating force and movement. The patient may be able to use residual voluntary muscle control for active support. In many cases the frequencies are raised up to 100 Hz, which would lead to a more continuous contraction in healthy subjects. Using frequencies beyond 20–35 Hz is not recommended in SCI subjects for muscle strengthening, since paralyzed muscles have longer twitch contraction times [80].

After this initial phase, FES-supported ergometer training is an option to enable active cycling using residual capabilities. The FES cycle moves the legs passively for a few minutes, before motion-synchronized FES at predefined intensities helps the patient to support the cycling movement voluntarily. FES is applied preferably to the gluteus maximus, quadriceps, biceps femoris, semitendinosus, tibialis anterior, and triceps surae muscles. The training should be repeated at least three times per week for 30 min for at least 3 months to prevent muscle atrophy. At least 12 months of training are required to maintain bone density [75, 77].

Patients with residual voluntary function in their lower extremities can be supported during ambulation with implantable or surface electrode-based FES systems. Reviews report improvement of ambulation during the FES application [81] and sometimes even lasting aftereffects when the system is removed, e.g., Ness L300 (Bioness Inc.). See also chapter 24 for more details.

Electrical Stimulation in Lower Motoneuron Type Paresis

Muscles paralyzed from lower motoneuron damage – typically observed in cervical SCI, conus, or cauda equina injury – can be activated only directly through ES of the paretic muscle. The used pulse width is roughly between 5 and 500 ms.

Lower motoneuron injury leads to a rapidly progressing muscle atrophy. Such denervated muscles contract after electrical single pulses, which slows down muscle atrophy. Daily treatment should begin as soon as possible after injury and should consist of several thousand impulses per day [82]. The objective to prevent muscle atrophy via ES is to maintain rather healthy muscle tissue in case nerve regeneration with consecutive muscle reinnervation takes place [82]. Continuing ES over even longer periods of time can reduce the risk to develop pressure sores [82]. The pulse width has to be chosen as long as necessary to elicit muscle contraction. However, an increasing pulse width can cause electrolysis-induced skin lesion right below the electrodes. Muscle fibers can recover after daily and intensive application of electrical pulses. With increasing excitability over time, pulse width can be reduced. The decreased pulse width allows higher stimulation frequencies, which are in particular suited to prevent atrophy of denervated muscles.

23.3.4.2 Conventional Physical Therapy

Overall, the goal of a restorative rehabilitation approach is to reinstall previously established sensorimotor functions such as standing and walking. Before and during task-specific interventions such as body-weight-supported treadmill training, basic prerequisites have to be addressed. Firstly, the patient needs to be stable in terms of

blood pressure, heart rate, and respiratory parameters. Secondly, individual muscles of the trunk and the lower extremities need to be strong enough to allow specific task-specific interventions. And finally, the overall balance needs to be reestablished for proper standing and walking function. Conventional physical therapy addresses specific components either individually or in combination. Unfortunately, the scientific literature provides very little evidence of most efficient physical therapy-based approaches.

Muscular Strengthening and Endurance

Arm and/or leg cycling helps to train muscular and cardiovascular endurance. Individuals with SCI can start during an early phase of their rehab regardless of whether they are bedridden or not. It is an appropriate method even if other activities, e.g., body-weight-supported treadmill training, are too exhausting. Moreover, arm and leg cycling can be practiced without therapist support. In preparation for bipedal locomotion, crawling and swimming improve endurance as well as the individual's inter-limb coordination skills. Rowing machines or cross-trainers can provide an aerobic benefit but, however, are challenging to use for SCI subjects. Respective patients need substantially spared motor function. In chronic SCI the recommended time to improve endurance is twice a week for at least 20 min each session [83].

A circuit training to strengthen an individual with incomplete SCI should involve weight machines at the beginning, because the guided movement is much easier to accomplish than working out with cable pulleys or free weights. Irrespective of the device used, every major muscle group should be addressed. It is recommended to increase strength by using 70-80 % of the individual maximal lift for 8–10 repetitions and 2–3 sets. For muscular endurance, moderate weight (60 % of the individual maximal lift) should be chosen for 15–20 repetitions and for 3 sets [84, 85].

The Major Muscle Groups and Their Appropriate Training Method (Table 23.6)

Trunk Stability and Balance

Strong shoulder and triceps muscles as well as sufficient upper body control/trunk stability in combination with walking aids such as crutches, canes, or walkers are important to compensate weaker lower extremities. Nevertheless, reasonably balanced loading of the feet has to occur, and overloading/overuse of the upper extremity should be avoided. If the patient has to carry more body weight with the arms

Table 23.6 Major muscle groups and exercise suggestions

Lower extremities Quadriceps, adductor, gluteus, hamstring, calve muscles	Leg press, squats, good mornings, calf/heel raises, lunges, crawl
Upper extremities Shoulder muscles, triceps and biceps muscles	Frontal/lateral pull down, (reverse) butterfly, rowing machine, biceps/triceps curl, push-ups, crawl
Trunk Back and abdominal muscles	Frontal/lateral pull down, reverse butterfly, rowing machine, crunches, swimmers, supermans, planks, push-ups, crawl

than with both feet or if it is too exhausting to keep the trunk in a straight position, body-weight-supported treadmill training should be preferred [3].

As pointed out crawling can help to practice inter-limb coordination in incomplete SCI individuals [86] asking for a reciprocal movement pattern (right hand and left knee, left hand and right knee). Forelimbs in animals and upper extremities in human subjects are linked to hind limbs/lower extremities through propriospinal neuronal pathways and have been shown to influence locomotor function both in quadrupeds as well as in bipeds [87, 88].

Balance training in SCI patients heavily depends on the neurological level of injury and the sensorimotor completeness. Therefore, the recommendations listed here describe basic concepts, which have to be adjusted for each patient. A good starting point to train balance is the sitting position ideally supported by both arms/hands and the feet on the ground. Assistance as needed to support the balance is provided. Incremental advances can be the removal of the arms for support, head turning, or catching objects while sitting. Introducing a knee-stand instead of the sitting position will get the more caudal sensorimotor system involved. Even more challenging for an SCI individual is the "one-knee-stand" due to a smaller supporting surface. More advanced exercises with a "Swiss ball" improve trunk balance and stability in incomplete SCI subjects.

The individual can be:

- Sitting on top of a "Swiss ball" with both feet on the ground
- Eyes open or closed
- Performing distal lateral flexion in the lower spine
- Planks or push-ups with both feet on the ball
- Both shoulders are on top of the "Swiss ball" with the hips straightened and both knees are in a 90° angle flexed/bent

Another way to work on the trunk balance, stability, and strength could be a Bodyblade®, different kind of swing sticks, or an adjustable crawler, which can be challenging and funny at the same time. Nearly every position gets tougher with a Bodyblade® or a swing stick – supine position, side plank, or a stand with feet shoulder wide apart. Using an adjustable crawler during therapy sessions is like a serious body workout and therefore should not be underestimated.

The following exercises can be realized by incomplete SCI individuals and some complete SCI individuals: Balance of the trunk can be trained by standing in a standing frame, which has adjustable degrees to tilt and turn (Fig. 23.7) or between parallel bars. The standing/balancing frame as displayed (Fig. 23.7) allows to shift weight from leg to leg and to train balance while being secured with a harness system.

The sequence of getting up can be facilitated in a stepwise fashion by raising the seat level, thus improving the patient's leverage reducing the effort and strength to perform the task. Alternatively, the harness of a body-weight-supported treadmill training can be employed to reduce the body weight and stabilize the trunk. For a comprehensive list of exercises, see www.physiotherapyexercises.com.

Fig. 23.7 Standing/balance trainer

23.3.4.3 Orthoses/Braces

A significant number of individuals with incomplete SCI, who recovered substantial sensorimotor function allowing them to walk, will need more energy performing the same movement. The walking distance might be decreased. Walking on uneven ground and overcoming obstacles become a much more challenging task due to impaired afferent input, strength, and coordination. In order to at least partially compensate for individual deficits, specific devices, namely, orthoses or braces, can be prescribed to SCI individuals. Moreover, orthotic treatment can help to prevent degenerative musculoskeletal changes due to muscular imbalance of nonphysiological joint load during gait.

Interdisciplinary Rehab Team

In accordance with the patient's expectations, skilled therapists and experienced rehab physicians define the required orthotic support using a variety of tests: strength, sensation, balance while standing, spasticity, stiffness, instability of joints, and range of motion at hips, knees, ankles, and trunk, as well as coordination. If a patient is able to take some steps, the clinicians will observe and evaluate spatial temporal gait parameters (velocity, cadence, step length, step time) and look for safety issues like toe clearance during swing phase and knee extension during stance phase. Orthotists should be involved in the rehab team to provide options for technical solutions to achieve the proposed rehabilitation goal. Orthotic prescriptions must be based on the abovementioned examinations, followed by the patient's biomechanical needs, and should be controlled frequently during the orthotic fitting and the therapeutical interventions. Because neurological improvement is likely to occur over time after an incomplete injury, the patient's needs may change over time, and the orthotic function needs to be adapted accordingly.

Orthotic devices are supposed to give better balance or stability, keep joints in a physiological alignment during stance phase, obtain clearance of the foot during swing phase, protect joints from nonphysiological kinematics and loads, and ensure stance stability and safety during standing and walking by compensating sensorimotor deficits. Nowadays, such devices are usually made of carbon fiber to reach

high stability at low weight. They may be off-the-shelf prefabricated orthoses or custom-made by an orthotist.

Orthotic Devices

Foot Orthoses (FO)

The main function of foot orthoses is to gain an optimized pressure distribution and to correct for malalignments (Fig. 23.8). Dynamic foot deformities, e.g., as a consequence of paretic tibialis anterior peroneal muscles, need to be corrected as far as possible. This leads to a stable base of support and must be seen as a crucial component of any orthotic solution. The stabilization of the foot structures allows for stable lever arms and has therefore a direct impact on the proximal biomechanical chain. In addition, FOs may support skeletal foot structures and thus compensate for weak intrinsic foot muscles. Nonphysiological loads can be avoided.

Ankle Orthoses (AO)

AOs provide dynamic lightweight support with a cushioned ankle wrap for mild drop feet (upper or lower motoneurons lesion), which supports dorsiflexion either via a plastic inlay fitting between the tongue and laces of the shoe or barefoot by using a hindfoot bandage instead of the shoe, which will be connected to the ankle wrap, respectively (e.g., Foot-Up® or Neurodyn Spastic®, Sporlastic Orthopaedics). The latter supports the foot up, corrects slight supination, acts against a plantar flexion using crossover elastic restraints, stabilizes the ankle joint, and prevents sprains by nonelastic lateral restraints. It is indispensable to adapt associated footwear and/or foot orthosis during dynamic fitting to allow an efficient gait and to compensate for typically seen foot deformities due to muscular imbalance.

Fig. 23.8 Foot orthosis: back side finally modified, front side basically adapted

Ankle-Foot Orthoses (AFO)

AFOs do involve the ankle and the foot. Depending on their construction, they can compensate for a drop foot with or without an active effect to the proximal joints, i.e., the knee and hip. This can be achieved by a construction, which includes a long orthotic forefoot and a ventral support at the proximal shank. The combination of a long forefoot lever arm with the ventral support induces a knee-extending moment and may support weak knee extensors during stance. A crouching gait can be avoided. Musculoskeletal deformities such as flexion contractures of the hips or knees and deformities of the trunk, e.g., scoliosis or torsional deformities of the lower extremities, can contribute to impaired gait, which cannot be compensated by AFOs.

AFO variations:

- Posterior leaf spring (Heidelberger Winkel)
  - Lightweight support for people with mild-to-moderate drop feet. These orthoses lift the foot off the ground during swing phase. It is not recommended for severe ankle-foot deformities (i.e., *pes equinus*), structural in- or eversion, or severe spasticity.
- Lightweight (carbon fiber) dynamic AFO
  - Lightweight support for people with mild-to-moderate drop feet (Fig. 23.9). Dynamic AFOs provide increased stability during stance including a knee-extending moment and thus moderately affect proximal joints, in particular

Fig. 23.9 Dynamic lightweight AFO

the knee joint. Control and support of plantar- and dorsiflexion is provided by energy-storing and energy-returning carbon fiber. Due to a defined shape and construction, these kinds of premanufactured orthoses (e.g., ToeOFF®, Camp Scandinavia) should not be used in patients with severe spasticity combined with structural deformities or people weighing more than 120 kg.

- Carbon fiber orthosis with hinge joints or dorsal leaf spring (GRAFO)

  – Ground reaction force AFOs (GRAFOs) aim to support body weight during stance. These custom-made carbon fiber orthoses may include adjustable hinge joints at the ankle with adjustable dorsoplantar stops and a spring to support foot lift. Hinge joints allow to define the range of motion with respect to the physical abilities and biomechanical needs (Fig. 23.10). Furthermore, hinge joints might be replaced by a stable carbon fiber dorsal leaf spring (Fig. 23.11). Springs are able to compensate for poor foot control in stance from initial contact on and are able to support the patient during terminal stance by energy return for an adequate push-off.

Knee-Ankle-Foot Orthoses (KAFO)

KAFOs are prescribed for patients with knee instability and/or insufficient knee extension due to paretic knee extensor muscles. In contrast to AFOs, the knee joint is included in the construction (Fig. 23.12). Pure knee instabilities in the coronal plane might be supported by free hinge joints – a good motor function (muscle strength 4) is required. The orthotic knee joint should be aligned with respect to the anatomical joint axis of rotation. A more posterior alignment leads to an increased

Fig. 23.10 GRAFO with adjustable hinge joint

Fig. 23.11 GRAFO with a carbon fiber dorsal leaf spring

Fig. 23.12 KAFO with swing phase lock joint (Fillauer LLC, Netherlands)

stability and supports knee extension slightly – with respect to the functional benefit an incongruent positioning is accepted in patients with insufficient knee extensors (muscle strength 3–4). Patients with more severe paresis of knee extensors (muscle strength ≤ 3) should be fitted with a manually locked knee joint. The lock compensates for the muscular weakness and keeps the knee joint in an extended position during stance. As a consequence the knee joint is also locked during stance and swing. The ipsilateral limb will be circumducted or the contralateral limb will be vaulted to achieve toe clearance during swing. It is obvious that this walking pattern will be rather inefficient and energy consuming. Modern components and orthotic knee joints Swing Phase Lock (Fillauer LLC, Netherlands, Fig. 23.12), E-Mag (Otto Bock, Germany), and Neurotronic (Fior & Gentz, Germany) have addressed this issue. The knee joint can be locked to provide stable stance. During swing it is unlocked to avoid the inefficient gait pattern. Depending on the model, the function is controlled mechanically or by a μ-processor unit. Both mechanical or electronic joint components in KAFOs require a specific gait training to take advantage of the full potential of these types of orthoses.

Neuroprostheses for Lower Extremities

Functional electrical stimulation (FES) integrated into an orthotic device (MyGait, OttoBock; Ness L300, Bioness Inc.) allows to stimulate paretic muscles to provide muscle contraction at the appropriate time point within a more complex movement cycle like walking. For example, the paretic tibialis anterior muscle (drop foot) will be activated externally by FES to provide an active dorsiflexion during swing. The combination of a sensor-based recognition of stance and swing in combination with FES allows for the coordinated toe lifting. A battery-powered signal generator stimulates the nerve transcutaneously via surface electrodes, corresponding muscles are activated, and a contraction occurs. Unpleasant sensations resulting from the transcutaneous stimulation represent a major limitation. Stimulating parameters can be adjusted to reduce such sensations. In contrast to conventional orthotic devices, the range of motion of the ankle joint is not affected by this neuroprosthesis. The patient is still able to perform active plantar flexion for a physiological push-off.

Nighttime Splinting

Nighttime splinting allows adequate positioning of major joints in lower and upper extremities in SCI patients. Respective measures can help to avoid contractures and structural deformities due to paretic muscles and spasticity. An example is a dynamic redression orthosis. Dynamic redression should be realized by low-load prolonged stretch. Dynamic spring control hinge joints help for a well-controlled force [89, 90]. Loss of sensation has to be considered to avoid skin lesions by the orthosis (Fig. 23.13).

Even with the administration of orthotic devices, balance and other “pre-gait” activities need to be performed before the actual gait training with/or without body-weight support can be initiated.

Fig. 23.13 Nighttime splint with dynamic spring-controlled hinge joints (Caroline, Germany)

23.3.4.4 Wearable Exoskeletons

Relatively new approaches to perform standing activities or reach-assisted walking in patients with motor complete spinal cord injuries are wearable exoskeletons. The devices include a frame and motor-driven gait orthosis to compensate any weakness of an individual's lower extremities and limited control of the joints. Different systems (e.g., Ekso GT, Ekso Bionics; ReWalk, Argo Medical Technologies; Indego, Parker Hannifin Corp) are available at the moment, and each system has pros and cons. All devices provide a reciprocal gait pattern. Some of them are able to trigger a step by shifting their weight to one side or notice a slight tilt of the individual's chest. The devices require the use of a walker or forearm crutches to maintain balance for standing and ambulation. The ultimate goals of these rather expensive devices is to allow activities in the standing position, to walk overground, to overcome obstacles (stairs, uneven terrain) and to improve the quality of life of SCI patients. However, at the moment respective devices are still being investigated and not yet established in the clinical or home routine. Appropriate trunk stability including sufficient upper extremity function to use crutches or a walker are required [91, 92].

23.3.5 Prevention/Management of Secondary Damage

Restorative rehabilitation therapies after SCI aim to retrain sensorimotor functions such as standing and walking as described in this chapter. Not all patients, which are introduced into a restorative rehabilitation program, will in the end regain sufficient independent walking function. This might be due to several factors such as too severe sensorimotor impairments, lack of fitness, comorbidities, disabling spasticity/pain and/or joint problems (contractures) [93]. Potential long-term complications related to impaired walking function such as joint deformities need to be considered and weighed against quality-of-life aspects [41].

Subsequent injuries after SCI constitute a significant problem. In a study, which included 1328 patients (AIS-A–D) at least 1 year after traumatic spinal cord injury, 19 % reported at least one injury within the last year, which required medical treatment. Patients with the ability to walk showed a high rate of injuries, not all of them related to falls [94]. Among 119 patients suffering from chronic incomplete SCI with a walking ability of at least 10 m, 75 % reported at least 1 fall irrespective of an accompanying injury within the last year. Most falls happened at home and in the majority of cases, patients only suffered slight injuries (bruises, scrapes, etc.). Of note, 18 % of the subjects reporting a fall suffered a bone fracture. Moreover, 45 % of the subjects who had fallen reported a reduced ability to get out into the community [95]. Dizziness, concomitant diseases (e.g., arthritis) and fear of falling increase the number of falls. In contrast, using a walker and regular exercises can reduce the number of falls [96]. In another study out of 515 ambulating subjects with chronic SCI 20 % reported at least one injury caused by a fall in the last year. Poor balance, the use of one crutch and the misuse of pain medication were associated with an increased rate of injury. If mobility was achieved equally through walking and wheelchair use the fall incidence was increased. In contrast, both predominant wheelchair users and predominant walkers showed a lower incidence of fall related injuries [97].

For these reasons, fall prevention should be given major consideration in therapy planning. Balance plays an important role since it represents the key to walk safely. In addition, it constitutes a predictor for walking quantity [4]. Therefore, therapy should include targeted balance training, as described above. Other approaches include targeted muscle training with strengthening of weaker muscle groups, practicing unfamiliar situations, regular evaluation of walking ability including checking the remaining deficits, and reevaluation for assistive devices. Only in exceptional cases unilateral walking support should be prescribed, e.g., if there are load limitations for one arm. If the risk/rate of falling is high and the walking velocity is rather low, patients should be advised to use a wheelchair as their prime mode of mobility. This does not exclude further gait training. However, training integrates the retained functions into activities related to transfers, changing positions in bed or relief from the wheelchair. Therapy must include fall training if walking is intended to be continued.

Clinical Case *A 75-year-old patient with traumatic SCI* (*NLI Th 12*, *AIS-D*, *8 weeks post-injury*) *covers a distance of 10 m with a walker requiring some assistance. The patient can urinate voluntarily*, *but suffers from a concomitant stress incontinence. She is not able to walk to the toilet in time on her own once she experiences the urge to urinate. After reassessing the therapy goals*, *wheelchair and transfer skill training – in particular transfer from the wheelchair to the toilet and undressing/dressing while standing – at the expense of locomotor training were intensified to allow for a higher level of independence*.

Another limiting factor to be considered is the presence of pain. The spine and all joints can be affected by pain. In the lower extremities, body-weight-related overloading due to insufficient muscular support is the main cause – in addition to preexisting joint damage. While an orthotic solution is possible for the knee and

ankle joints, this proves difficult for the hip joint and the trunk. Assistive devices can be helpful to compensate for paretic limbs, thus maintaining walking function. In most instances, this approach will challenge the musculoskeletal integrity of the upper extremities, in particular the shoulder girdle. In 14 ambulating individuals with incomplete SCI the strain on their shoulder joints during walking with crutches or a walker was examined. The strain on the shoulder joints was extremely high in both instances – use of crutches or walker – with a greater strain being observed using crutches. Surprisingly, the load peaks were even higher than the forces needed to propel a wheelchair [98]. A survey in 783 people with incomplete SCI highlights the relevance of this aspect. 66 % of the interviewed SCI individuals use at least one assistive device (walker, crutches, canes, braces, support person) [99]. Interestingly, individuals using the wheelchair more infrequently reported more pain and fatigue in comparison to frequent wheelchair users or walkers. These findings support the notion that incomplete SCI patients can only maintain walking function at the expense of increased effort and energy consumption in order to compensate for sensorimotor deficits [93, 99]. In terms of therapeutic consequences, the following aspects should be considered: if pain occurs or increases, the cause needs to be identified and adequately addressed (use/modification of orthotic devices/braces, walking with body-weight support, training individual components responsible for pain). The use of pain medication is an option, if the treatment is transient. Otherwise it needs to be weighed against the risk to mask functional weaknesses, which can promote longer lasting musculoskeletal problems. As pointed out before, balance will be affected by pain medication and can thus increase the risk of falls [97].

In this context, orthoses/braces, in particular correcting orthoses, should also be carefully monitored. Respective devices can causes or propagate pain [99]. Furthermore, in particular in areas with severe sensory deficits, pronounced muscular atrophy or existing contractures the risk of pressure ulcers has to be weighed against the benefit of orthoses/braces.

It should be emphasized that gait training during the acute phase bears the risk to raise false expectations that cannot be achieved in the end. Therefore, regular reevaluation of the therapeutic goals and consecutive readjustments are mandatory, which have to be discussed with the patient to properly plan the therapeutic interventions to obtain skills required for everyday life (e.g., wheelchair mobility). After all, the end justified the means. If sufficient mobility can be achieved through wheelchair use, but not through walking, an important goal determining quality of life has been achieved [93, 100].

23.4 Adjunct Therapies for the Modulation of Neuronal Activity

Most of the neurorehabilitative therapies for restoration of the ambulatory function are based on the neuroplasticity of the CNS. Neuroplastic changes meaning adaptation of neural networks to an injury of the spinal fiber tracts may occur at different levels of the CNS, starting with the peripheral, musculoskeletal system, continuing

at the level of the motor and interneurons of the spinal cord and ending at supraspinal levels such as the brainstem and the cortex [101]. Although it is not clear, to which degree the reorganization of neuronal structures and changes in the synaptic transmission at different levels contribute to the improvement of function, there is growing evidence that stimulation methods modifying the activity of neural networks at spinal and cortical level may enhance the outcomes of task-oriented therapies [102–104]. Noninvasive techniques offer the possibility to be used early in the rehabilitation of individuals with incomplete SCI due to the ease of application and the relatively low price of the technical equipment and can therefore effectively be integrated as adjunct therapies into activity-based training regimes. The basic principle of activity-modulating therapies is depending on the selection of the stimulation parameters: On the one hand, an inhibitory effect may reduce spastic activity and thereby allowing a better use of residual voluntary motor functions. On the other hand, the general activity level of neuronal networks might be increased providing the ground for a faster and more effective learning and a higher persistence of motor functions.

The most widely used and best investigated noninvasive activity-modulating therapies are noninvasive brain stimulation techniques, namely, transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), and, on the spinal level, transcutaneous spinal cord stimulation (tSCS) activating dorsal, afferent spinal roots of lumbar segments.

TMS is a noninvasive, easy-to-apply method that utilizes a wired coil to produce a powerful and rapidly changing magnetic field, which passes the bony structures of the skull and produces small electrical currents in the region of the brain just under the coil via electromagnetic induction. These currents in turn elicit action potentials in neurons of the targeted area. TMS with single impulses and the associated measurement of motor evoked potentials in limb muscles have become a widely used neurophysiological tool both in clinics as well as in research [105]. When using TMS of the motor cortex in a repetitive manner (rTMS), a frequency-dependent effect occurs: while low-frequency (1 Hz) rTMS inhibits cortical excitability, high-frequency (5–20 Hz, in theta-bust stimulation up to 50 Hz) rTMS produces an increase in cortical excitability, which can facilitate motor sequence learning. Although the number of studies is low, a recent study was able to show the superiority of a combination of a gait rehabilitation program and 15 sessions of a 20Hz-rTMS over the primary leg motor area versus a sham rTMS. A significant improvement was observed after the last rTMS session in the active group for Lower Extremity Motor Score (LEMS), walking speed, and spasticity. Improvement in walking speed was maintained during a 2 week follow-up period. Sham stimulation did not induce any improvement in LEMS, gait assessment, and spasticity after the last session and neither during follow-up. More research is necessary to optimize rTMS parameters and to adapt the therapy to the individual impairment caused by the SCI [106, 107].

Although the use of direct currents for therapeutic purposes dates back the nineteenth century, tDCS has been systematically investigated in early 2000 [108]. It offers the possibility to change cortical excitability in a polarity-specific manner

(anodal versus cathodal) and this can be achieved by the application of electrodes with different polarity to different locations on the surface of the skull to excite the underlying neural tissue. tDCS effects are most likely induced by membrane polarization, altering the firing rates of neurons. Anodal tDCS induces depolarization, while cathodal tDCS induces hyperpolarization, so that anodal stimulation produces excitation and cathodal stimulation produces inhibition. tDCS can be easily integrated into neurorehabilitation because of the cheap equipment, ease of application and high acceptance of the non-perceptable currents by patients. The few results of the use of tDCS for enhancement of a locomotor therapy are controversial, underlying the need for better definition of effective training parameters and adequately powered randomized studies to prove the therapeutic superiority [109, 110].

Another exciting method currently under investigation is the use of transcutaneous spinal cord stimulation. In contrast to the preceding methods, which target brain structures, tSCS is aiming at modulating the state of the lumbosacral spinal circuitry either for reduction of spasticity [111] or for supporting the effects of locomotor training approaches [112]. The basic principle of SCS is that lumbar posterior roots can be activated by transabdominal electrical currents so that a frequency-dependent modulatory effect occurs. While stimulation frequencies of 30 Hz led to an augmentation of voluntary residual muscle activities in individuals, higher frequencies of 50 Hz showed a reduction of reflex activity and muscle tone. Both effects contributed to a better ambulatory function in individuals with chronic incomplete SCI. Like in rTMS and tDCS clinical studies involving a larger number of end users need to be conducted to clearly show the efficacy and general usefulness of this method.

Although there are many open questions about neural activity-modulating therapies regarding the selection of safe and most efficient parameters, combinatorial therapeutic approaches will most likely boost the success of neurorehabilitation and lead in the end to a increased quality of life in persons living with the consequences of SCI.

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Neuroprosthetics

24

Rüdiger Rupp

Abstract

Neuroprostheses based on functional electrical stimulation (FES) are a means for compensation of lost motor functions such as grasping or walking. Many prerequisites need to be fulfilled for successful use of a neuroprosthesis, most importantly a low degree of lower motor neuron damage, an unrestricted passive joint motion, and a negligible spasticity.

For improvement of the grasp function, neuroprostheses with different degrees of complexity and invasiveness exist. The systems available for routine clinical application have demonstrated functional benefits and improvement of the users' independence and quality of life. Hybrid neuroprostheses combining FES with orthoses hold promise for restoring completely lost upper extremity function. Novel user interfaces integrating biosignals from different sources are needed to make full use of their many degrees of freedom. Brain-computer interfaces are an emerging technology that may serve as a valuable adjunct to traditional interfaces.

The main barrier for everyday use of lower extremity neuroprostheses solely based on FES is the occurrence of rapid muscle fatigue due to a non-physiological spatial and temporal activation by FES. However, their combined use with semi-active gait orthoses or robotic exoskeletons promises to overcome some of the current limitations.

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Novel developments for more selective stimulation of neurons or for activation of the lumbosacral spinal pattern generator network may enhance the functionality of future neuroprostheses. It is likely that upcoming neuroregenerative therapies will be able to restore some motor functions. In these cases, modular, personalized, and patient-cooperative neuroprostheses will be needed for integration in and support of the residual body functions.

24.1 Introduction

The loss of motor function is the most obvious consequence of a spinal cord injury (SCI). Functional limitations resulting from SCI limit the affected individuals' ability to live independently and retain gainful employment post-injury [13, 49]. People with SCI also tend to report a lower quality of life compared to able-bodied persons [7]. Currently, 40–50 % of all individuals with an SCI are tetraplegic due to injuries of the cervical spinal cord with resulting life-long paralysis of the lower and upper extremities. While the majority of tetraplegic patients have a neurological level of lesion at C4 and C5 with loss of hand and finger function, the most common lesion level in paraplegic patients is Th12 with preserved trunk stability but loss of functions of the lower extremities [79].

Bilateral loss of the grasp function leads to a substantial dependency of tetraplegic patients on caregivers. Therefore, one of the main priorities of these patients is to improve a missing grasping and reaching function [2, 101]. Paraplegic patients rate the restoration of walking as very important [16]. If there is sufficient voluntary control of muscles caudal to the level of lesion, surgical procedures such as muscle and tendon transfers, tenodeses, and arthrodeses can be successfully applied for regaining a meaningful upper and lower extremity function [39, 48, 97]. However, if no voluntary motor functions are present or an individual is unwilling to undergo surgery with the associated extended postsurgical rehabilitation period, neuroprostheses on the basis of functional electrical stimulation (FES) may represent a valid alternative for functional restoration [87]. In general, neuroprostheses are technical systems that use electrical impulses to compensate for the loss of motor functions after lesions of the central nervous system.

The aim of this chapter is to provide the background to understand the physiological principles of and clinical prerequisites for the application of neuroprostheses, their possibilities and challenges for compensation of lost upper as well as lower extremity function, and the promises of future developments.

24.2 Electrical Activation of Nerves and Muscles

The transfer of information within the nervous system is based on the generation of action potentials and their transmission between excitable cells. In the physiological condition, an action potential on an axon is triggered by temporal and spatial

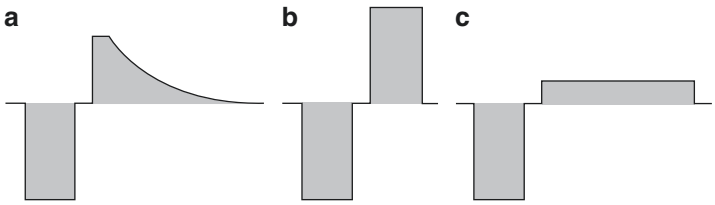

Fig. 24.1 Typical FES stimulation waveforms. (**a**) Rectangular pulse with exponential charge balance pulse. (**b**) Biphasic rectangular pulse. (**c**) Biphasic, rectangular pulse with reduced amplitude, but increased width of charge balance pulse

summation of electrical potentials on postsynaptic membranes. However, it is also possible to depolarize the membrane voltage of a nerve at a certain location by external electrical impulses to such a degree that a physiological action potential originates from there. From an electrical viewpoint, the nerve membrane mainly represents a capacitor, whose voltage is proportional to the injected charge. To guarantee a robust generation of action potentials despite time-varying and unknown skin tissue and inner tissue impedances, constant-current impulses are applied.

In electrical stimulators intended for FES applications, the initial stimulation impulse is followed by a charge balance pulse (charge = current × time, gray area in Fig. 24.1) to avoid a net transmission of charged ions in the tissue under the electrodes. By this the coagulation (anode) and colliquation (cathode) necrosis, which typically occurred in prolonged application of FES with the technology available in the mid 1970s, can be effectively avoided. A low amount of charge injection is tolerated by the tissue as long as the effective direct current density at the electrode stays below 35 μA/mm^2 [95].

From a technical viewpoint, the exponential charge balance pulse (Fig. 24.1a) can be implemented in the simplest way by adding a series capacitor to the stimulation circuit. The generation of rectangular pulses is technically more complex but allows for a higher pulse repetition rate (= stimulation frequency in Hz) (Fig. 24.1b). In case of pulse widths below 300 μs, a short pause of approx. 100 μs is inserted between the stimulation and charge balance pulse. Without this pause the activation effect of the stimulation pulse is partly reduced due to the steep rise of the charge balance pulse [110]. If the amplitude of the charge balance pulse is substantially lower compared to the stimulation pulse (Fig. 24.1c), the pause can be omitted without any detrimental effect.

Basically, by FES an action potential can be triggered at any location of the nerve fiber – from the neuron via the axon to the motor end plate – which is then transmitted like in the physiological condition to the effector organ. It does not make a difference, if the stimulation impulses triggering the action potential are applied via surface electrodes, percutaneous wire electrodes, or fully implanted electrodes, which are places on a muscle or directly at the nerve's axon.

Usually, for stimulation of innervated muscles, biphasic, charge-balanced rectangular impulses with a stimulation pulse width between 50 and 500 μs are used.

If innervated muscles are activated by electrically induced nerve action potentials, a relatively small amount of charge is needed (curve 4 in Fig. 24.2). A much higher charge is needed in case of direct stimulation of denervated muscle fibers, because the motor threshold of muscle membranes is 500–1000 times higher than the activation threshold of nerve membranes [5]. Even in the case of needle electrodes inserted directly into an innervated muscle, it is always the nerve and not the muscle fibers that are electrically activated. This is the reason why the term "muscle stimulation," which is clinically often used in the context of innervated muscles, is misleading.

With a larger extent of and longer time after denervation, more charge is needed to directly activate denervated muscles (curve 3 and 2 in Fig. 24.2). In case of a completely denervated muscle, impulses with high amplitude and pulse width need to be injected to generate contractions (curve 1 in Fig. 24.2) with the danger of exceeding the maximum permissible current density for surface electrodes of 2 mA/cm^2 and the associated risk for local burns [50]. In any case, stimulated denervated muscles do not produce the same amount of force than innervated ones. Therefore, a careful screening for the presence of denervated muscles is mandatory to estimate the potential of a user for successful application of a neuroprosthesis. In Europe, a few stimulators are commercially available capable of generating short (<1 ms) impulses for stimulation of innervated muscles and long impulses (>100 ms) for

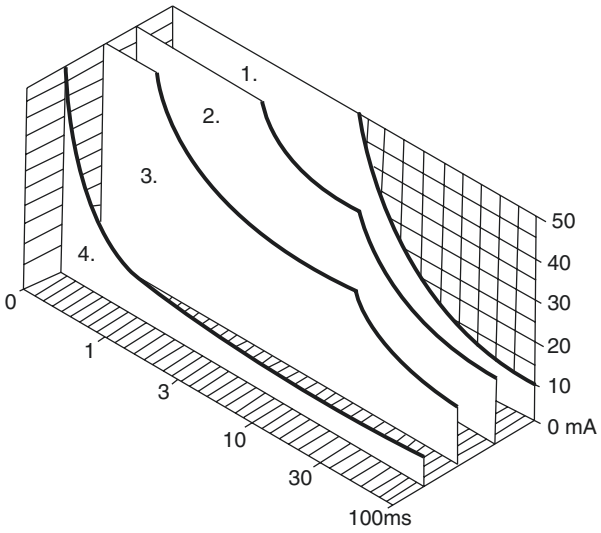

Fig. 24.2 Strength-duration curves of rectangular pulses for completely innervated (*4.*), decreasingly innervated (*3.*, *2.*), and completely denervated muscles (*1.*) [28]. The strength-duration curve shows the minimal current amplitude at a given pulse width, which is necessary to elicit a muscle twitch

direct muscle stimulation. With these devices, a precise testing of the innervation status of muscles and a training of denervated muscles to prevent muscle degeneration can be performed. Examples of such devices are the portable, single-channel Paresestim FES system from Medel GmbH, Hamburg, Germany, and the two-channel system stimulette den2x from Dr. Schuhfried Medizintechnik GmbH, Vienna, Austria.

The strength-duration curve for neural and muscle membrane flattens out with long stimulus durations, reaching an asymptote called rheobase. When the stimulus strength is below the rheobase, stimulation is ineffective even when stimulus duration is very long. The minimum pulse width needed to elicit a muscle contraction with a current of two times of the rheobase is defined as chronaxie. Both the rheobase and chronaxie are useful to document the degree of denervation and the course of reinnervation of a muscle.

Although electrically induced action potentials basically comply with physiological activation mechanisms, there are relevant differences between the physiological and artificial generation of muscle contractions [102]: In the physiological condition, if low muscle forces are generated, mainly thin fibers are activated. With increasing force, more thick fibers are recruited (Fig. 24.3). In case of external electrical stimulation, thick nerve fibers are first activated due to their higher electrical field and voltage gradient, and with increasing force, also smaller fibers get involved.

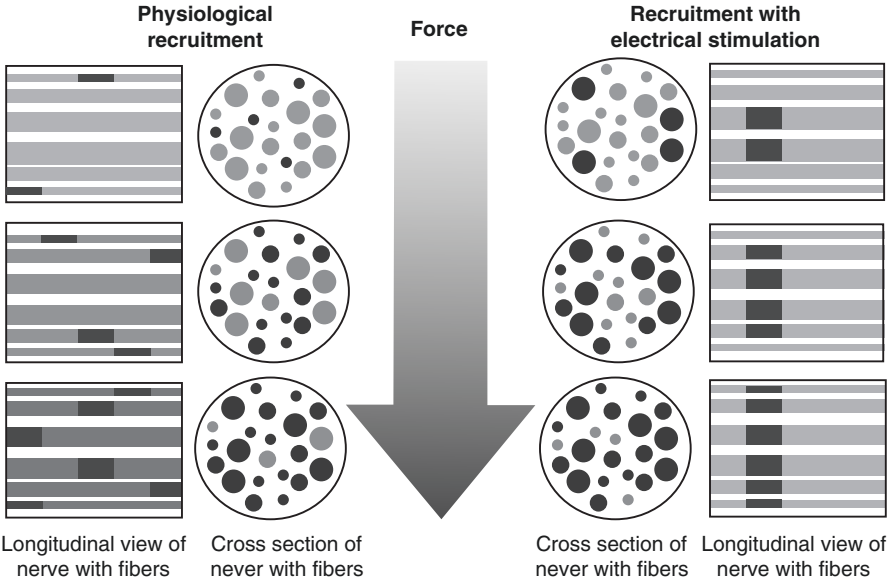

Fig. 24.3 Recruitment of nerve fibers under physiological conditions and by electrical stimulation. *Dark areas* represent activated parts of nerves; *light gray areas* indicate inactive parts

However, thick nerve fibers end at fast-fatiguing muscle fibers, while thin fibers innervate more fatigue-resistant muscle fibers. This phenomenon is called "inverse recruitment" [82] and represents one of the main causes why stimulated muscles fatigue relatively fast compared to the physiological condition. In addition, all nerve fibers get activated nearly at the same time, which results in an almost synchronous activation of all muscles fibers of the corresponding motor units. Furthermore, each electrical impulse activates the same motor units. The inverse recruitment together with the synchronous activation of the same motor units causes a rapid fatigue of stimulated muscles. Basically, muscle fatigue occurs more quickly with higher rates of pulse repetition. Therefore, in practical FES applications, where tetanic contractions are needed, relatively low stimulation frequencies in the range of 16–20 Hz are used that allow for generation of a sufficient amount of force without having too much tremor. Nevertheless, continuous tetanic stimulation contractions at high force levels, e.g., needed for standing and walking, can only be generated over a short time period of 15–30 min depending on the amount of training. Additionally, the movements and forces generated by FES are less graduated when compared to the physiological condition. This is especially the case when low forces for fine control of hand and finger movements are needed.

In patients with chronic SCI, paralyzed muscles consist to a large extent of fast-fatiguing muscle fibers with the associated severely decreased fatigue resistance and capability for force generation. The disuse atrophy of paralyzed muscles can be reversed through FES training even many years after SCI. Additionally, FES training converts the fiber composition of muscles in the direction of slow fatiguing muscles [94].

24.3 SCI-Associated Conditions Limiting Neuroprosthetic Applications

In general, FES may not be applied in individuals with metal implants in the stimulated areas of the body or if active implants such as cardiac pacemakers or medication pumps are present. Besides these non-SCI-related exclusion criteria, a lot of secondary side effects associated with SCI may prevent the successful use of a neuroprosthesis. A thorough initial screening is mandatory to set up a realistic roadmap for each prospective neuroprosthesis user.

In individuals with paraplegia due to a lesion of the conus or cauda equina, damage to the lower motor neurons and/or their axons occurs. The presence of denervated muscles may prevent a successful application of neuroprosthesis. As stated before, stimulated denervated, flaccid muscles do not produce enough force to effectively contribute to a functional restoration sufficient for everyday use [50].

Individuals with a cervical SCI have a very heterogeneous neurological and functional status depending on the level, completeness, and type of lesion [11, 105]. Additionally, in about 30–50 % of individuals with tetraplegia, denervated muscles

are present to a more or less extent due to the damage of motor neurons directly at the lesion site [26, 74].

Within the first 2 weeks after SCI, spasticity develops in many patients. Spasticity or clonus may be triggered by electrical stimulation in particular at the beginning of the FES training and each FES session. However, after some FES sessions, the muscle tone may be successfully reduced by the training [63].

If motor impairments persist, they lead to other negative effects. Immobility may lead to a reduction of the passive range of motion of affected joints, which may result in severe contractures with totally immobile joints due to calcified capsules. In such cases, even a strongly stimulated muscle is not able to generate joint movements. Intensive physical therapy may help to prevent some of these negative side effects on the musculoskeletal body structures.

In the chronic stage, profound disuse atrophy of the permanently paralyzed muscles is present. This may be reversed in innervated muscles by an FES-based training; however, if the SCI persists over a long time, it may take some months to achieve a fatigue resistance and force sufficient for neuroprosthetic applications [33].

Autonomic dysreflexia (AD) is a potentially dangerous clinical syndrome that develops in individuals with SCI, resulting in acute, uncontrolled hypertension. Briefly, AD develops within the first 6 months after injury in individuals with a neurologic level at or above the sixth thoracic level (T6). The occurrence of AD increases as the patient evolves from spinal shock. AD prevalence rates vary, but the generally accepted rate is above 50 % of all individuals with injuries at T6 and above. Patients with a sensorimotor complete injury have a much higher incidence of AD (91 % with complete injury vs. 27 % with incomplete injury) [22]. AD is caused by the damage of sympathetic spinal fibers and the resulting imbalanced innervation of the autonomous nervous system. Episodes of AD can be triggered by any strong stimulus below the level of injury [62]. AD may also be triggered by electrical stimulation of the lower extremity [4], but has also been seen by the author in very high lesioned patients during the application of a grasp neuroprosthesis.

Pain is a major problem after SCI and most of the patients report to have pain. In the acute phase after an SCI, it is mainly nociceptive pain due to trauma or spasm [30]. Usually within the first year after the injury, neuropathic pain develops in about 40–50 % of the patients and tends to become chronic [99]. Paresthesia in the stimulated dermatomes may restrict the application of a neuroprosthesis particularly systems based on surface electrodes.

24.4 Upper Extremity Neuroprostheses

Over the past 30 years, FES systems for restoration of upper extremity function with different levels of complexity and degree of invasiveness have been developed. While a handful of systems for restoration of a lost or restricted grasping function

have reached a level of maturity sufficient for routine application in end users with tetraplegia [85], none is available for restoration of a lost reaching function suitable for everyday use.

24.4.1 Grasp Neuroprostheses

When using FES in a compensatory setup, the easiest way to improve a weak or lost grasp function is to apply multiple surface electrodes. Generally, their major advantages are their simple and safe application and that they can be offered to patients for temporary application at a very early stage of rehabilitation. During this phase the electrode setup has often to be adapted to the changing neurological condition due to spontaneous recovery. Additionally, costs of noninvasive systems are much lower than those of invasive neuroprostheses, and they can be applied by physical medicine and rehabilitation specialists without the need for surgical expertise [21]. Examples of noninvasive grasp neuroprostheses are (1) the commercially available NESS H200 System (formerly known as Handmaster, Bioness Inc., Valencia, CA, USA), which is mainly intended for training purposes, but can also be used as an assistive device for support of activities of daily living [1], and (2) the formerly commercially available Bionic Glove for improving the strength of a tenodesis grip in SCI individuals with preserved strong voluntary wrist extension [84]. Other more sophisticated prototypes in terms of control capabilities were successfully evaluated in the clinical setting, but are not available for home-based application [69, 106].

The main aim of the application of a grasp neuroprosthesis is to generate two grasp patterns, namely, the lateral grasp, also called key or pinch grasp, and the palmar grasp, also called cylinder or power grasp. The lateral grasp provides the ability to pick up flat objects between the flexed fingers and the flexing thumb, while the palmar grasp, in which the thumb is positioned in opposition to the index finger, permits larger objects to be handled. To generate these grasp patterns, electrodes on the thenar eminence and inside the hand are typically needed, which, however, tend to fall off or shift easily due to the extended skin and soft tissue movements in these areas [29]. However, with seven self-adhesive gel electrodes placed on dedicated positions on the forearm (Fig. 24.4a), the pinch and power grasp patterns can be restored without the need for electrodes on the hand [92]. The pinch grasp can be achieved by stimulation of the finger (ext. digitorum communis muscle, electrode pair (EP) 1 in Fig. 24.4a) and thumb (ext. pollicis longus, EP 2 in Fig. 24.4a) extensor muscles for hand opening, the finger flexors (flex. digitorum superficialis, flex. digitorum profundus) for hand closing and the thumb flexor (flex. pollicis longus) for grasping. In many SCI end users, it is possible to stimulate the flexor muscles of the fingers and the thumb with a common electrode pair (EP 3 in Fig. 24.4a). By implementation of a dedicated stimulation profile into a universally programmable, multichannel FES stimulator available from different vendors (e.g., Motionstim 8, Medel GmbH, Hamburg, Germany), it is possible to use co-contractions of the thumb flexor and extensor muscles to achieve a state, in which the fingers are sufficiently flexed and the thumb is still in an extended position. For the power grasp,

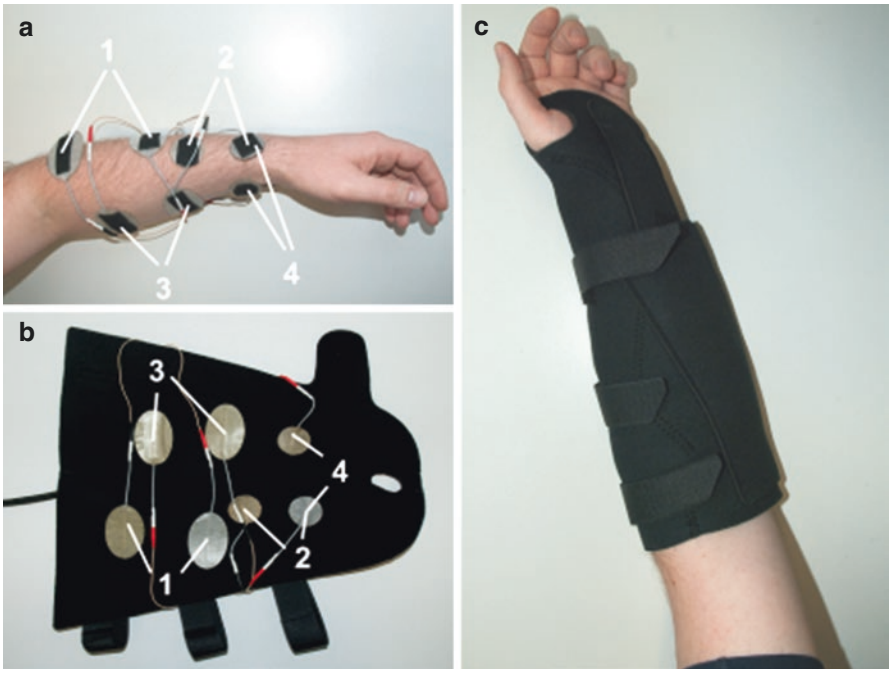

Fig. 24.4 (**a**) Electrode positions together with the assigned channel numbers of the stimulator. Due to space limitations, *channel 2* (ext. pollicis muscle) and *channel 4* (opponens pollicis muscle) share a common electrode. (**b**) Electrodes fixed with a velcro strap in a personalized forearm sleeve for easy and quick electrode mounting. (**c**) Mounted forearm sleeve. To stabilize the wrist, a bent metal splint is integrated into the volar part of the sleeve

a branch of the median nerve innervating the opponens pollicis muscle can be selectively stimulated with an electrode pair (EP 4 in Fig. 24.4a) placed on the medial side of the forearm.

Apparent disadvantages of grasp neuroprostheses based on surface electrodes include difficulties with daily reproduction of the desired grasping movements and limited selectivity in stimulating deeper or small muscles. Additionally, patients consider the placement of the electrodes to be complicated [54]. Some of these limitations may be overcome by an adjunct fixation mechanism in the form of an orthosis or a sleeve. After the appropriate electrode positions have to be defined, a self-adhesive velcro strip is stuck on the top of the electrodes, which are then covered by a neoprene sleeve. This sleeve is manufactured according to the individual anatomy (proximal and distal diameter, length, position of the thumb) of the forearm (Fig. 24.4b). The velcro strips hold the electrodes in a fixed position in the sleeve, which dramatically reduces the time for donning. The sleeve contains a hole for the thumb and a mark sign at the proximal end, which facilitates the correct positioning of the sleeve on a daily basis (Fig. 24.4c).

As a precondition for a functional grasp, the wrist needs to be stabilized in neutral position during flexion of the fingers. In individuals with preserved elbow

Fig. 24.5 (**a**) Individual with cervical SCI and absent finger and thumb function writes with an ordinary ball pen. (**b**) Individual moves glass cylinder (120 g). (**c**) Eating a cookie. (**d**) Grasping a coin. (**e**) Holding a matchbox to light a match. (**f**) Manipulating a can

flexion, the wrist extensor muscle is often weak or denervated. In these cases, it is not possible to achieve a stable dorsal extension of the wrist by stimulation, and a fixation splint made of aluminum is integrated into the sleeve to maintain the wrist in neutral position during grasping. With this setup, a variety of activities of daily living (ADLs) can be performed by the users (Fig. 24.5).

Another problem of noninvasive grasp neuroprostheses is the huge variation of the grasp patterns in dependence of the wrist rotation angle. In addition, defining the optimal size of stimulation electrodes during initial setup is often time-consuming. A promising concept for faster determination of the desired electrode positions and the dynamic compensation of position-dependent relocation of electrodes is the use of electrode arrays, in which small electrodes can be selectively activated and dynamically merged to virtual electrodes [41, 68, 83]. However, the clinical value of this newly introduced concept needs to be evaluated in future studies involving a larger number of end users.

Despite the technological progress made over the last two decades, some of the disadvantages of noninvasive neuroprostheses persist, among them are limited excitability of deeper muscle groups, painful sensations in case of paresthesia in the stimulated parts of the body, and handling problems. As a consequence, implantable neuroprostheses have been developed with different degrees of complexity: the BION [46, 67], a small single-channel microstimulator that can be injected through a cannula; a stimulus router system [31], an implantable electrode that picks up the current from surface electrodes; a multichannel implantable stimulator [100]; as well as a modular, networked, and wirelessly controlled system for stimulation and sensing [113]. In contrast to cardiac pacemakers, implants for restoration of complex motor functions need to deliver large amounts of energy to reanimate paralyzed limbs. This energy is typically provided through an inductive link either during operation (Freehand) or for charging batteries inside the implant (BION 3). Therefore, external coils need to be placed on the skin over the implant, and users of implanted motor neuroprostheses usually need to carry external components with them (Fig. 24.6c).

One of the implantable grasp neuroprostheses – the Freehand system – achieved commercialization in 1997 and was successfully used throughout the world by over 300 individuals with an SCI at C5/C6. It is therefore the most widespread implantable neuroprosthesis for restoration of the grasp function [47]. The first version of the Freehand system consisted of an implantable electrical stimulator, whose metal housing serves as a common anode (Fig. 24.6a, b), with eight stimulation channels and an external control unit, which contains the central processing unit and the batteries. In the early years, it used epimysial electrodes, which needed to be sutured to the muscle surface, but later it was possible to use intramuscular electrodes, which were directly inserted into a muscle and self-secured themselves with hooks. In the most recent revision, it is equipped with 12 stimulation channels and provides four channels for registration of myoelectric signals for control purposes [37].

The results of a multicenter trial including 51 Freehand users impressively demonstrated its high level of functional efficacy, end user satisfaction [80], and economic benefits [21]. Despite the proven clinical success, its commercialization stopped in 2001. This fact clearly demonstrates the difficulties industry encounters in sustained transfer of technology due to the small number of prospective end users and the few institutions providing the infrastructure for successful implantation of invasive neuroprostheses and for postoperative rehabilitation.

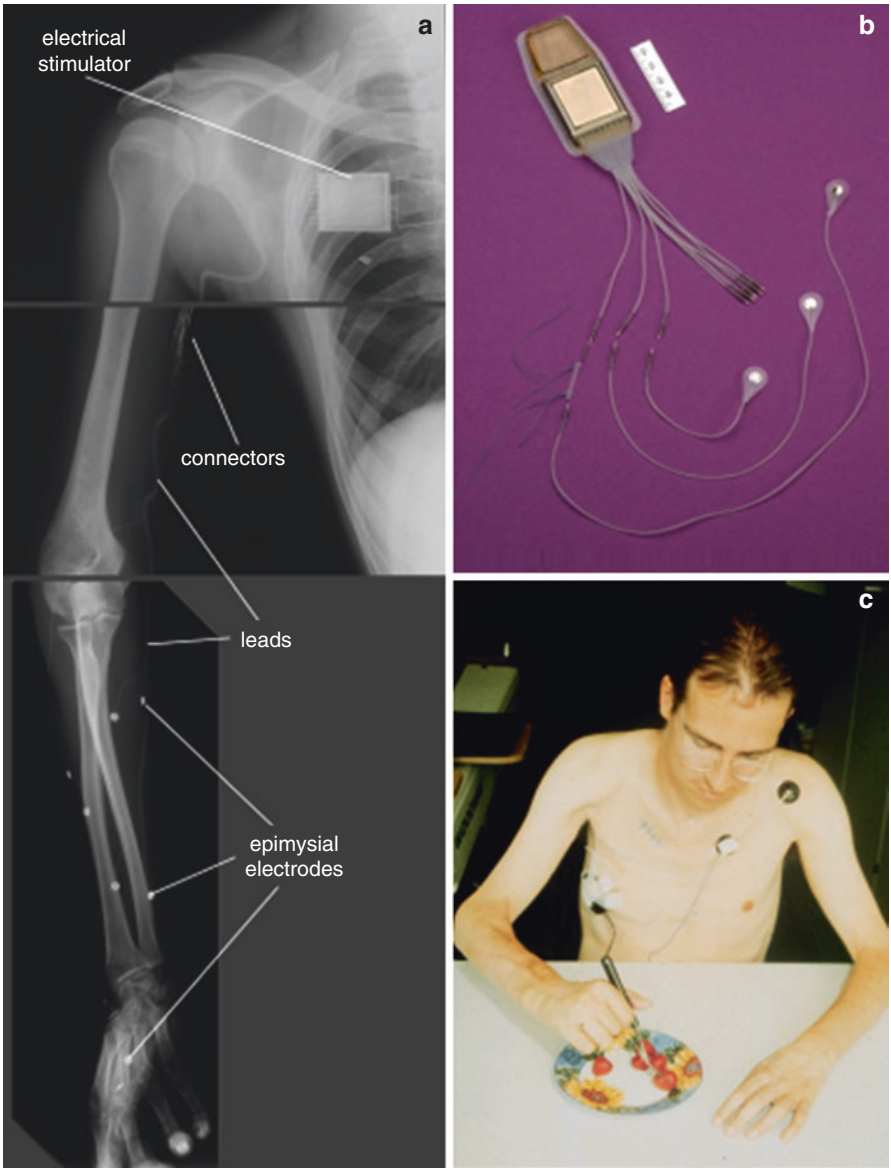

Fig. 24.6 (**a**) X-ray of internal components of the Freehand neuroprosthesis in the right arm of an end user. (**b**) Implantable electrical stimulator with connectors, leads, and epimysial electrodes. (**c**) User eating with the Freehand system. The external shoulder joystick (left shoulder) and induction coil (right chest) are visible. The external control unit containing the microprocessor and batteries is not shown

Besides their high costs, implantable systems inherently harbor the risk of infections and general surgery-related risks. Complex revision surgeries are necessary in case an implanted component fails. Although it has been shown that these events occur rather rarely [53], this risk has to be clearly communicated to patients who decide to receive an implant. Due to the fact that implantable neuroprosthesis and systems based on surface electrodes have distinct advantages and disadvantages, they represent alternative rather than competitive devices to surface electrode based systems.

Despite all the technical progress achieved, it has to be clearly stated that the degree of functional restoration by the currently available neuroprostheses based either on surface or implantable electrodes is rather limited. Even with the most sophisticated systems, it is only possible to restore one or two grasp patterns, and this does not include independent activation of single fingers or joints [52, 113]. Nevertheless, despite all their restrictions, grasp neuroprostheses represent a proven method for improving quality of life of end users with preserved shoulder function and elbow flexion, but missing hand and finger function.

24.4.2 Hybrid Neuroprosthesis for Grasping and Reaching

Most of the current neuroprostheses for the upper extremity are foreseen for individuals with preserved shoulder function and elbow flexion. In case of completely lost upper extremity function, meaningful restoration of a reaching and grasping function for activities of daily living by means of neuroprosthesis has not yet been demonstrated. The feasibility of using percutaneous electrodes for restoration of elbow extension and shoulder flexion/abduction was investigated only in an experimental setting [20, 45]. Recently, two advanced Freehand stimulators providing in total 24 simulation channels connected to either epimysial, intramuscular, or nerve cuff electrodes were successfully implanted in two individuals with an SCI above C4 [71]. Although shoulder, elbow, forearm, wrist, and hand movements were achieved in both subjects by this highly invasive and complex surgical approach, only one individual was able to perform two activities of daily living (scratching nose, shaking hands).

In general, a major problem in restoration of a completely lost upper extremity function is the rapid muscle fatigue of continuously stimulated shoulder and elbow muscles. To assist weak voluntary or stimulated shoulder forces, a mobile, passive, spring-based antigravity arm support system mounted on the wheelchair may be used [71, 81]. To avoid fatigue of stimulated muscles, so-called hybrid neuroprostheses consisting of a combination of FES and orthoses are proposed. In general, an orthosis is a mechanical device that fits to a limb and corrects a pathological joint function. An actively driven orthosis supports the joint movements with active electric or pneumatic actuators. The disadvantages of these exoskeletons are their mechanical complexity, limited possibility for home-based use in an ordinary everyday scenario, and their need for a sufficient power supply [96, 111]. Therefore,

these systems are mainly intended to be applied in users for whom sufficient movements cannot be generated by FES.

If sufficient joint movements can be generated by FES, the application of an orthosis with an electromechanically un-/lockable joint is a more efficient solution than a robotic exoskeleton. In its released state, this joint allows for free movements and keeps a fixed joint position in the locked state. This locked state helps to avoid fatigue of the stimulated muscles needed to maintain a stable joint position. Both types of FES-hybrid orthoses may expand the group of prospective users of an upper extremity neuroprosthesis in the future.

At this point, it must be emphasized that the neurological status and functional capabilities of individuals with SCI, even with the same level of injury, vary to a large degree. As a consequence, an upper extremity neuroprosthesis necessarily has to consist of several modules that can be personalized according to the capabilities, needs, and priorities of an end user. Though this fact is well known among the neuroscience [9] and assistive technology community [44], very few technical solutions incorporate it [89].

For achieving a meaningful capability for object manipulation in individuals with an SCI at C4 or higher with only a few residual arm movements preserved, a mobile robot arm mounted on the wheelchair may be a cheaper, more robust, and better performing alternative than a full upper-arm neuroprosthesis based on FES. Some of these robot arms have been successfully tested in everyday scenarios in persons with tetraplegia, and some are commercially available, e.g., the iArm from Exact Dynamics, Didam, the Netherlands, and the Jaco arm from Kinova Robotics, Quebec, Canada. Whether these robotic arms are accepted by their users and an improvement of quality of life can be achieved in the long run, needs to be shown in future studies involving a larger number of end users.

24.4.3 User Interfaces for Control of Upper Extremity Neuroprostheses

The reliability and performance of the user interface of a neuroprosthesis have the same impact on the users' acceptance as the meaningfulness of the FES-generated movements. Therefore, a robust user interface is a highly important component of a neuroprosthetic system. While users may be satisfied with a switch-based control scheme for step initiation of a lower extremity neuroprosthesis, the need for a sophisticated user interface for autonomous control of grasping is much higher in upper extremity neuroprostheses. The individual selection of the control method is mainly depending on the nature and degree of preserved functions under voluntary control of a user. The following functions may be used as command sources:

1. Movements of mouth and tongue, including speech
2. Voluntary movements or electrical activity of muscles not directly related to the function to be restored, e.g., movements or myoelectric activities of the contralateral shoulder or head movements

3. Voluntary movements or electrical activity of muscles directly involved in the function to be restored, e.g., wrist extension or weak muscles of the forearm
4. Specific cortical electrical activities

Speech control has not gained wide acceptance for neuroprosthesis control due to slow speed, long delays, and maloperation in noisy environments [77]. The use of tongue movements [43] or tooth clicks [32] may restrict the users' ability to communicate. All user interfaces relying on mouth control are not appropriate if users wish to eat or drink with the help of the neuroprosthesis.

24.5 User Interfaces Using Functions Not Related to the Restored Movements

An established control method is the use of preserved movements not directly involved in the grasping function. Examples are the use of head orientation [115] or shoulder movements [100]. Command interfaces based on head movements or eye gaze may interfere with the user's natural eye movements. These may differ substantially from those of healthy subjects, since users with SCI need to compensate the loss of tactile and proprioceptive feedback by visual feedback. Nevertheless, head movements or eye gaze may be applied successfully when combined with other input modalities such as preserved myoelectric activities of the shoulder [19].

Shoulder movements recorded by a two-axis shoulder position sensor were chosen as the standard input modality of the user interface of the implantable Freehand neuroprosthesis [100]. The degree of hand opening/closing and the force of the closed hand are normally controlled by the user through forward/backward movements of the contralateral shoulder in a proportional manner. Locking of the grasping position is initiated by a quick shoulder upward movement. An additional switch button is integrated into the shoulder joystick, which permits the user to switch between grasp patterns through a short press and the in-/activation of the entire system through a long press. In case shoulder movements are restricted due to muscular weakness or joint contractures, also electromyographic (EMG) signals from voluntarily activated muscles can also be used for control [38]. The performance of EMG- and movement-based control is at least for short-term use in the same range.

24.6 User Interfaces Using Activities of Muscles Directly Involved in the Restored Movements

For bilateral grasp restoration, the use of shoulder movements for neuroprosthesis control is limited, because shoulder movements are needed to place the hand correctly in space and, in so doing, interfere with the control function. An alternative involves using muscles that do not interfere with any upper extremity task. In some users, muscular functions below the level of injury, e.g., from the lower extremities, that are not functionally relevant may be used for control [73]. A promising

way to set up a universal control interface involves selective activation of ear muscles [71, 109].

All of the control modalities mentioned above share the fact that the control is not "natural" for a user, i.e., it requires a substantial amount of training and special attention during use, particularly in the first weeks of use [38]. To overcome this limitation, the use of movements or muscle activities directly involved in the reaching or grasping function has been proposed. One of the first implementations of this approach was a proportional control of hand grasp by the degree of wrist extension measured either noninvasively [86] or by an implanted Hall-effect-based wrist angle sensor [8]. However, some users who are able to fully extend their wrist despite the presence of strongly stimulated finger flexors may not actually need a neuroprosthesis, if they use a natural tenodesis grip (passive flexion of finger and thumb flexors by active extension of the wrist) for everyday tasks.

A highly promising approach for a more natural and intuitive control involves monitoring the activity of weak muscles of the hand and arm. An example of this type of control is the use of the EMG activity of a weak brachioradialis or ext. carpi radialis longus muscle for proportional control of the grasp strength [51, 93, 106].

In individuals with high, complete SCI and the associated severe disabilities, too few residual functions may be preserved for setup of a reliable user interface. This has been a major limitation for the development of a reaching neuroprosthesis for individuals with a loss not only of hand and finger but also of elbow and shoulder function. Additionally, even end users who are basically able to use a certain interface may not be able to remain in control over an extended period of time due to physical and mental fatigue. Therefore, it is crucial for users to have a choice of options and for rehabilitation professionals to make them available, since each individual will find that some of the available options are more productive and work better than others. In this sense, brain-computer interfaces (BCIs) may serve as an alternative human-machine interface or may provide an additional control channel as an adjunct to traditional user interfaces.

24.7 Brain-Computer Interfaces for Control of Upper Extremity Neuroprostheses

BCIs are technical systems that provide a direct connection between the human brain and a computer. These kinds of systems are able to detect thought-modulated changes in brain activity and transform the changes into control signals. Most of the BCI systems rely on bioelectrical brain signals that are recorded noninvasively by electrodes on the scalp (electroencephalogram, EEG). A BCI system consists of five sequential components: (1) signal acquisition, (2) feature extraction, (3) feature translation, and (4) classification output, which interfaces to assistive devices and generates (5) a feedback to the user. These components are controlled by an operating protocol that defines the onset and timing of operation, the details of signal

processing, the nature of the device commands, and the oversight of performance [98]. At present, EEG-based BCI systems can function in most environments with relatively inexpensive equipment and therefore offer the possibility of practical BCIs in end users' home environment.

One type of EEG-based BCI exploits the modulation of sensorimotor rhythms (SMRs). These rhythms are oscillations in the EEG occurring in the alpha (8–12 Hz) and beta (13–30 Hz) bands and can be recorded over sensorimotor areas on the scalp. Their amplitude typically decreases during actual movement and similarly during mental rehearsal of movements (motor imagery, MI) [78]. It is known that people can learn to modulate the SMR amplitude by practicing MI of simple movements, e.g., hand/foot movements. This process occurs in a closed loop, meaning that the system recognizes, with the help of machine learning methods, the SMR amplitude changes induced evoked by MI, and these classification results are instantaneously fed back to the users. With the help of the feedback, users can adapt their mental modulation strategy to improve classification results. These neurofeedback-based procedure and mutual human-machine adaptation enable BCI users to control their SMR activity and use these modulations to control output device [15]. Although, most BCIs are used to generate binary control signals, MI-BCIs allow the detection of an intended movement based on brain signals, making them an exciting option for natural control of a grasping and reaching neuroprosthesis control, in particular in individuals with high SCI.

In the first pioneering work in BCI-controlled grasp neuroprosthesis, the BCI was used in a mainly digital manner ("brain switch") as a substitute for the traditional neuroprosthesis control [76]. A novel development in BCI research is the introduction of the hybrid BCI concept [75]. A hybrid BCI (hBCI) consists of a combination of several BCIs or a BCI with other input devices. These input devices may be based on the registration of biosignals other than brain signals, such as EMG activities, or signals from traditional input devices like joysticks or mouses.

In a first single-case study, a combination of an MI-BCI and an analog shoulder position sensor was proposed [90]. With upward/downward movements of the shoulder, the user was able to control the degree of elbow extension/flexion or of hand opening/closing. The selection, if the analog signal from the shoulder position sensor is used for elbow or hand control, and the access to a pause state were determined by the brain switch provided by the MI-BCI.

With this setup, a highly paralyzed end user who had no preserved voluntary elbow, hand, or finger movements was able to perform several activities of daily living, among them eating a pretzel stick, signing a document, and eating an ice cream cone (Fig. 24.7), which he was not able to perform without the neuroprosthesis. He used short imaginations of movements of the right hand to switch from hand to elbow control or vice versa. A longer imagination led to a pause state with stimulation turned off or reactivated the system from the pause state.

Despite research on the use of BCIs for neuroprosthesis control has seen tremendous progress in recent years, BCIs are not yet ready for independent home use. In general, setting up and handling current BCI systems is relatively complicated compared to traditional user interfaces and requires the (tele-)presence of technical

Fig. 24.7 Sequence of pictures showing the eating of an ice cream cone with the support of a FES-hybrid orthosis in a user with completely lost elbow, wrist, and hand function (**a**). The user starts in the hand control mode and lifts his left shoulder to open the right hand for grasping the ice cone (**b**, **c**). After successfully grasping the ice cone, the user emits a BCI command to switch from hand control to elbow control and lifts his shoulder to flex his elbow (**d**). Now, the user licks the ice. Finally, the user lowers his left shoulder to extend the elbow on (**e**), he puts the cone in its original place and switches back to hand mode to release the ice cream cone on (**f**)

experts. Thus, BCIs have to be improved to a stage at which end users together with their caregivers are able to apply the systems independently at home. A key component for achieving this goal is the availability of easier to handle, gel-less electrodes that provide a sufficient signal quality. Additionally, more studies with people in real need for a BCI such as individuals with high cervical SCI are needed to determine if research results obtained in able-bodied subjects also apply to neurologically impaired end users [91].

Initial human applications of invasive BCIs, in particular of intracortical electrode arrays for single-neuron recording, indicate that an intuitive brain control of robotic arms is possible without the need for extensive learning [17, 40]. However, this technology has not yet demonstrated its long-term stability over years. Additionally, due to the small number of study participants, the extent to which the results can be generalized remains unclear [103].

24.8 Lower Extremity Neuroprostheses

The first work reporting on the successful use of FES for restoration of foot dorsiflexion was already published in 1961 [66]. Since then a variety of FES systems have been developed and are commercially available for drop foot stimulation. While the use of FES for compensation of a limited movement of a single joint like the ankle is rather simple, the restoration of a completely lost lower extremity function is much more complicated, and many research groups worldwide have been working on the development of practical lower extremity neuroprostheses since decades.

24.8.1 Standing and Walking Neuroprostheses

A breakthrough in the development of lower extremity neuroprostheses using surface electrodes was achieved in 1970, where two Slovenian researchers used electrical stimulation of the peroneal nerve in individuals with complete paraplegia to elicit the withdrawal reflex with the associated flexion of the hip, knee, and ankle joints thereby simulating the swing phase of walking [59–61]. By this they overcame the problem that hip flexor muscles cannot be stimulated sufficiently directly by surface electrodes. If the stimulation of the withdrawal reflex is combined with the stimulation of the quadriceps and the glutei muscles, walking, standing up, and sitting down are possible with only six pairs of electrodes. Based on this knowledge, several devices have been developed, from which a few are commercially available, e.g., the Motionstim from Medel GmbH, Hamburg, Germany, and the Parastep FES system from Sigmedics Inc., Fairborn, Ohio, USA, which has been on the market for over 25 years. The Parastep system is used in combination with a walking frame with integrated push buttons for manual step initiation and has been tested so far in more than 750 individuals with complete thoracic injuries. The results of the Parastep applications show that performance in respect to walking in community is

rather limited [55] but that positive therapeutic benefits in terms of cardiovascular training and overall quality of life can be achieved [35].

After the feasibility of surface FES systems was shown, they were continuously improved: A higher number of stimulation channels were implemented for achieving a smoother standing up and sitting down, for combined antagonistic and agonistic stimulation to avoid hyperextension of the knees, and for stabilization of the trunk. Sensors were integrated for detection of gait phases and for automatic initiation of steps by recording of muscular activity of trunk muscles [34]. However, despite all these efforts, lower extremity neuroprostheses based on surface electrodes never made it to routine clinical use. One of the main reasons for this is the complicated and time-demanding setup of multiple stimulation electrodes, in particular the self-placements of electrodes on the glutei muscles.

To overcome the handling problems of surface FES systems, invasive neuroprostheses either based on percutaneous electrodes or fully implantable systems have been developed. At the end of the 1970s, up to 30 percutaneous electrodes were injected in each leg of volunteers with the aim of mimicking the physiological activation of lower extremity muscles [70]. With this overall high number of electrodes and the use of multiple electrodes in one muscle, a surprisingly smooth walking pattern was achieved. However, research in this direction was abandoned because of a missing perspective for everyday use and severe infections in some study participants due to broken wire electrodes. Over the last 40 years, different fully implantable systems were developed; however, none of them has become commercially available yet. Starting with the implantation of an 8-channel system for restoration of standing and walking in a few individuals with complete paraplegia in 1982 in Vienna, Austria [104], later a 16-channel system consisting of two Freehand implants [57] was used by the Cleveland group. In 2001, a 24-channel system was used from the European SUAW (stand-up-and-walk) consortium [112] in two paraplegic volunteers for the same purpose. With these implantations, it was successfully shown that the handling problems of neuroprostheses for walking based on surface electrodes can be overcome and a high reproducibility of movements can be achieved.

However, the main limitation of all lower extremity neuroprostheses independent from the technology and level of invasiveness is muscular fatigue. Due to the high forces needed to carry the full body weight and the co-contractions of agonistic and antagonistic muscles during standing, fast fatigue of stimulated muscles occurs allowing users only to walk very short distances of approx. 50–100 steps. The upright body position inherently bears the risk for falls. Therefore, the use of a walking frame, a walker, or crutches for stabilization of the trunk is mandatory, which restricts the use of the hands. In the early applications, lower forces were generated by stimulation that needed to be compensated by the users by carrying more weight on the crutches or the walker. However, on a long term, this led to shoulder pain, and as a consequence, the neuroprosthesis was sooner or later abandoned by the users.

At the current state of the art, lower extremity neuroprostheses do not represent an alternative to the wheelchair. Noninvasive FES systems are mainly used for therapeutic purposes to maintain joint mobility, muscle mass, and local vascularization.

The latter contribute effectively to the prevention of pressure ulcers. Fully implantable systems are used in everyday life mainly not for walking but for standing and transfers from and into the wheelchair. A good example for this paradigm shift is the VA/CWRU Standing System from the Cleveland group. This extremity neuroprosthesis evolved from the former 16-channel walking system and uses an 8-channel Freehand electrical stimulator with intramuscular electrodes in the quadriceps, glutei, and lumbar erector spinae muscles bilaterally for restoration of standing [108]. This system has been implanted in 15 users with paraplegia, who report a positive impact on their perceived quality of life [88]. However, studies are urgently needed to obtain quantitative information on the costs and implantation risks on the one hand and economic and personal benefit on the other. In any case, the technology of lower extremity neuroprostheses is after at least three decades of research and development still not mature enough to be broadly used for improvement of mobility in everyday life.

24.8.2 Hybrid FES Systems and Exoskeletons

During the last decade, neuroprosthesis for compensation of a lost lower extremity function was built solely on the basis of FES, because FES incorporates the body's own resources for energy-efficient activation of muscles. Additionally, the regular use of FES has positive therapeutic effects in regard to joint mobility, spasticity, cardiovascular training, and maintaining bone density. However, the two major technological challenges in solely FES-based lower extremity neuroprostheses are (1) the short application times due to the fast fatigue of muscles as a consequence of the need for continuous stimulation even during standing and (2) difficulties in generating precise kinematic patterns due the nonlinear activation characteristics of muscles and the huge delays between onset of electrical stimulation and generation of force. To overcome these problems, a combination of FES with an external orthosis is proposed [24]. While these orthoses were fully passive in the early years, they are now either electromechanically un-/lockable [56], variably dampered [12], or actively driven by electrical or pneumatical actuators [36]. The advantage of an orthosis is that a stable joint position can be maintained without the need for FES-induced co-contractions of agonists and antagonists. Additionally, joints can be linked with each other either mechanically or electrically, thereby allowing for simple generation of predefined multijoint kinematics. While the first reciprocating gait orthoses of the 1950s looked very bulky and were very heavy, the field of orthotics has tremendously emerged throughout the last years. The introduction of new lightweight materials such as aluminum and carbon has led to customizable high-end solutions with an improved functionality and appearance. The latter is highly important for increased users' acceptance and compliance.

A technical challenge of hybrid neuroprostheses is the need for sophisticated control concepts, which are able to adequately manage the balance between the muscular forces generated by FES or by the actuators of the exoskeleton [23].

Although the beneficial therapeutic effects of FES are known, from a pure technical perspective, it is much easier to achieve ambulation in individuals with complete paraplegia by the use of robotic exoskeletons. The progress made in rechargeable battery technology over the last years, the availability of low-power, high-performance microprocessors, and the introduction of energy- and space-efficient electrical drives boosted the development of robotic exoskeletons for compensation of walking, standing, and partially also for stair climbing. Some robotic exoskeletons have become commercially available, among them the Ekso (Ekso Bionics, Richmond, CA, USA), the Hybrid-Assistive Limb (HAL) 5 (Cyberdyne, Tsukuba, Japan), the Indego (Parker Hannifin, Cleveland, OH, USA), the Rex (Rex Bionics, Auckland, New Zealand), and the ReWalk (ReWalk Robotics, Yokneam Ilit, Israel) systems [18]. Although some of them are intended to be used for gait training in a clinical setting, some are specifically designed to be used as personal assistive devices. Robotic exoskeletons are compared to hybrid neuroprostheses easier to handle by the users themselves. In particular, the setup time of the device and time for donning and doffing are much shorter. Nevertheless, even with the most sophisticated systems, users have to fulfill several requirements for a successful use. In any case users need to have sufficient trunk control. For most devices, the ability to hold crutches for additional stabilization and for turning needs to be preserved. The range of motion of the lower extremity joints must be unrestricted and the degree of spasticity must be low. Although data on the safe use of robotic exoskeletons are available for most devices, the long-term musculoskeletal complications and the level of users' acceptance need to be determined in future studies.

24.9 Future Developments and Challenges

The main restriction of lower extremity neuroprosthesis is the fast fatigue of muscles due to the synchronous stimulation of nerves and the limited ability to activate individual motor units. Also upper extremity neuroprostheses would profit from higher selectivity, because fine-graded movements of individual fingers may be possible. To achieve a more selective activation of nerves closer to the physiological condition, novel concepts for stimulation of peripheral nerves are developed. Another promising approach for improving the performance of neuroprostheses for walking and standing is the stimulation of the spinal circuitry called spinal or central pattern generator for locomotion located in the lumbar spinal cord. This network of interneurons is capable of interpreting afferent input from the lower extremities and of generating locomotor-like stepping movements [42].

24.9.1 Novel Concepts for Peripheral Nerve Stimulation

A higher selectivity in stimulating peripheral nerves can only be achieved by the use of nerve electrodes. As a general rule, a higher degree of selectivity is associated

with a higher level of invasiveness and as a consequence a higher risk for damage to neural structures [25]. Intramuscular or epimysial electrodes have a negligible risk for causing any harm during first-time implantations and revision surgeries. Multipolar nerve cuff electrodes, which are placed around a nerve, provide a higher selectivity than muscle electrodes, but with a higher risk for complications. This is in particular true, if the electrodes are not flexible and connective tissue grows in the space between the nerve and the electrode resulting in denervation of motor units. The highest level of selectivity is achieved with intrafascicular [64] or nerve-penetrating electrodes [14]. However, these electrodes cannot be used without causing damage to nerve structures during implantation. If such highly invasive electrodes are implanted at a location, at which the nerve is exposed to extensive mechanical stretching, additional mechanical damage or tissue reactions due to chronic inflammation are likely to occur over time. To avoid these problems, multichannel electrodes might be placed more proximally, ideally at the ventral spinal roots, or even inside the gray matter of the ventral horn of the spinal cord. The latter is the basis for the promising concept of intraspinal microstimulation (ISMS) [6]. For ISMS, microwires are inserted near lower motor neurons, which are stimulated by microampere currents. While ISMS has been extensively tested in animal experiments, it still awaits its first human application.

With smaller dimensions of electrodes, the likelihood of exceeding a critical current density at the electrode-tissue interface is getting higher resulting in necrosis and chronic inflammation. While this may not be relevant for neural recording systems, it represents the major barrier for the use of micro- and ultraminiature electrodes for electrical stimulation. Due to a not perfect balancing of the injected charge, corrosion may occur at the surface of the electrodes degrading their electrical conductivity over time. In case of chronic inflammation, activated macrophages may additionally contribute to this effect.

A solution for overcoming the limitations of electrical activation of single axons or nerve cells may evolve from a relatively new method called optogenetics. This approach is based on the identification and functional characterization of several photoactivated ion channels, which have the remarkable property of being light gated [10]. Through introduction of a single gene-encoding channel rhododopsin-2 (ChR-2), a light-gated activation of neurons was realized. It was demonstrated that light-gated activity in ChR-2-positive neurons has a rapid onset in the millisecond timescale and is highly consistent while being phase locked to the stimulus frequency. Since photo-stimulation is noncontact and can be genetically targeted to specific cell populations using viral-vector gene therapy, a much higher spatial specificity in three dimensions can be achieved than in electrical stimulation opening up the possibility of large-scale spatial-temporal patterned stimulation for neuromodulation [58]. Optogenetics may also offer a seamless solution to the problem of cross talk generated by simultaneous electrical stimulation and recording. Although the perspective of human application of these methods is fascinating, the clinical translation of the combination of genetics and optics, including photonics, will face several challenges, in particular the unknown long-term effects of the genetically modified cell populations [114].

24.9.2 Spinal Cord Stimulation

Another very promising approach for restoration of the lower extremity function is the direct stimulation of the lumbosacral spinal cord either with epidural electrodes, typically used for pain relief, or by use of transversal surface stimulation [72]. It is assumed that the afferent fibers of the posterior roots are stimulated with both types of stimulation, thereby modulating the activity of the lumbosacral spinal circuitry [65]. It was demonstrated in the mid 1990s in individuals with clinically complete SCI that there is a stimulation frequency-dependent effect on the motor pattern of the spinal pattern generator [27]. High frequencies around 25–35 Hz facilitated a stepping-like motor pattern, while frequencies around 10–16 Hz produced extensor contractions similar to those that occur during standing. It has been recently shown in four individuals with an initially clinically motor complete SCI that voluntary motor function can recover after a combined application of epidural stimulation of different sites of the lumbosacral spinal cord and task-specific standing and locomotion training [3]. The study clearly shows that neuromodulation of the subthreshold motor state of excitability of the lumbosacral spinal networks was the key to recovery of intentional movement, because activity-based therapy applied over a month before the implantation of the epidural electrode did not lead to any improvement. However, since some input from the brainstem must be preserved to voluntarily trigger a stepping pattern and the exact mechanisms for the observed functional recovery are still unknown, it is not clear in how far the results obtained in four study participant can be generalized to a larger population. Additionally, more research is necessary to find ways for generation of stronger contractions in the lower extremities to allow for independent locomotion.

Conclusion

Over the past 30 years, about 25 neuroprostheses with different electrode technologies, degree of complexity, and level of invasiveness have been developed. Less than five of them have successfully applied in a larger group of end users, while others were only tested exemplarily with a few subjects. Lower extremity neuroprostheses for standing, walking, and stair climbing have not yet reached a level of usability sufficient for independent home use. Grasp neuroprostheses demonstrated in several clinical trials that they can greatly increase the quality of life of users with completely missing hand and finger function, in whom surgical options such as tendon transfers are not applicable.

From a technological viewpoint, scalable, modular neuroprostheses are a prerequisite for providing users with a personalized assistive device that is adapted to the residual capabilities, limitations, and needs of each individual end user. This issue of implementation of personalized and user-cooperative neuroprostheses will become more relevant in the future, if neuroregenerative therapies will succeed in increasing the number of individuals with preserved motor functions. With hybrid neuroprostheses combining orthotic and FES components, a further improvement in the functionality of neuroprostheses in particular for

compensation of the loss of the lower extremity function and an extension of the group of prospective users will be achieved. In this context, invasive and noninvasive neuroprostheses are companions rather than competitors, because a substantial percentage of individuals with SCI are unwilling to undergo implantation surgery. Prospective neuroprosthetic users need to be transparently informed about the additional benefits, risks, and long-term complications of implantable neuroprostheses compared to the noninvasive solutions.

During the development of neuroprostheses, it has become obvious that the functionality of the user interface has the same impact on the level of user acceptance than the actuator components. BCIs are a highly promising method for intuitive control of neuroprostheses, and research in this field has seen tremendous progress in recent years. The new concept of the hybrid BCI holds the promise that BCIs can be seamlessly integrated into traditional user interfaces such as switches, joysticks, EMG sensors, or eyetrackers and represents a major step toward user-cooperative neuroprostheses. Initial studies incorporating the hybrid BCI approach show that one configuration does not work with all end users. Similar to the orthotic and stimulation components of a neuroprosthesis, the possibility of a personalized configuration of the user control interface will be essential for its successful acceptance and integration in the users' everyday life. Long-term studies are needed with end users in real need of a BCI-controlled neuroprosthesis to demonstrate its reliability and usefulness.

Special care must be taken to correctly identify end users who may profit from a grasp neuroprosthesis. Spasticity, restrictions in joint mobility, and lower motor neuron damage are major obstacles for successful application of a neuroprosthesis. In general, the capabilities and limitations of the currently available systems need to be clearly communicated to users waiting for a "cure" and to be aligned with their needs and expectations to avoid disappointment and frustration.

During the last decade, a higher affinity to personal and wearable technology evolved in the general community due to the widespread utilization of smartphones, navigation systems, and augmented reality systems. This is also true for persons with motor impairments such as amputees. Nowadays, a sophisticated prostheses or orthosis is perceived more as an expression of personal uniqueness rather than a device for compensation of a handicap. This change in attitude to assistive devices might help to overcome the complacency in individuals with SCI and professionals with the standard of care and may lead to a better compliance with and acceptance of high-tech solutions like neuroprostheses. Additionally, an integration of neurotechnology into educational curricula or training programs to certify health-care professionals like physicians or physiotherapist and occupational therapist is needed to increase knowledge about its possibilities and limitations.

In any case, an industrial uptake of the available technology is necessary to achieve a broad availability of neuroprostheses for routine clinical application and to guarantee long-term support for end users, including provision of spare parts and consumables. Together with the difficulties of regular reimbursement,

this seems to be one of the main barriers for widespread application of neuroprostheses in general, which have not been overcome during the last 20 years [107]. Multidisciplinary teams of engineers, health-care providers, consumers, and reimbursement agencies need to bring in their expertise and unique perspectives and keep up an intensive dialogue to remove the current barriers. Traditional rehabilitation team boundaries will need to be expanded to establish neuroprostheses as routinely used assistive technology.

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Translation: Relevance of Spinal Cord Injury Animal Models

25

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Abstract

There are currently no therapeutic interventions available for the treatment of spinal cord injury (SCI). The discovery and validation of the growing number of promising therapies will require continued reliance on preclinical animal models of SCI prior to human translation. Animal models of SCI are instrumental in better understanding the mechanisms involved in traumatic SCI and evaluating the efficacy of therapeutic interventions. Over the past 40 years, substantial gains have been made in developing consistent, reproducible and reliable animal SCI models.

These models vary in terms of the species utilized, injury location, and injury mechanism, each with its own advantages and disadvantages. While the controlled experimental environment of preclinical studies is considered advantageous, it is this that makes animal models distinct from clinical reality, where there is considerable heterogeneity in baseline health and injury mechanics. The challenge then, is to evaluate what level of preclinical evidence is sufficient to proceed with clinical trials. The range of experimental paradigms available to the scientific community give new opportunities to address translational questions prior to human testing. Continued open communication involving scientists, clinicians, regulatory agencies, funding agencies, and the individuals living with SCI is required to move forward efficiently towards the establishment of novel therapeutics for the treatment of SCI.

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25.1 Introduction

Each year, more than 10,000 individuals in North America and many thousands more around the globe are paralyzed after sustaining an acute spinal cord injury (SCI) (see chapter 1), leaving them to endure one of the most physically and psychologically devastating injuries known to mankind. More than four decades of passionate research in this field have generated substantial progress in understanding the mechanisms that underlie SCI pathology. Alongside this, a growing number of therapeutic interventions have shown promise in animal models of SCI and are vying for human translation [81].

While the optimism surrounding clinical translation reflects significant scientific progress, there are also important challenges that extend beyond the decision to move a promising experimental therapy 'from bench to bedside'. While a handful of drug therapies have emerged from the laboratory to be tested in humans with acute SCI, none have succeeded in demonstrating convincing neurological benefit in large-scale clinical trials [26, 57, 82, 97]. These past clinical trials in acute SCI have highlighted the significant time and tremendous resources required for completion. For example, the clinical evaluation of Sygen for acute SCI occurred over a 14-year period from the initiation of a phase I study to the completion of its multicentre phase III randomized trial [31, 32] and required the collective efforts of over 20 neurotrauma centres in North America. The heterogeneity of human SCI necessitates the recruitment of large numbers of patients for adequately powered clinical trials, which is challenging due to the relatively low incidence of traumatic SCI (see chapter 20).

Given the considerable time, financial, and personnel resources required to complete a clinical trial, it is hard to argue against the need for demonstrating robust efficacy of a therapy in preclinical studies prior to embarking upon a clinical trial. *But how much is enough*? *Does the animal species utilized for such experiments matter*? *Does the injury paradigm matter*? *What preclinical pieces of evidence that a therapy actually* '*works*' *need to be assembled to establish a persuasive rationale to move forward with human translation*? While efforts have been made to create an objective method for evaluating the 'translational readiness' of potentially promising SCI therapies [53], there are no widely agreed upon criteria to determine when a treatment has received enough preclinical evidence to justify large-scale clinical trials. In part, this is related to the fact that we do not have examples of treatments proven to be efficacious in human trials that then enable us to look back at how they were evaluated preclinically. In the absence of such guidance, the field depends on animal models of SCI to evaluate the robustness of therapies prior to human translation, with the hope of improving the likelihood of success in clinical trials.

25.2 History of Translation in SCI

Clinical trials of interventions that aim to improve neurological function after SCI can take many years to complete [25, 56, 87, 97, 98] and cost an enormous amount of money, as recently illustrated by Geron Corporation's decision to prematurely

terminate their embryonic stem cell trial [29] (see chapter 21). While the SCI community absorbs these direct costs of the clinical trial, it also bears the potential opportunity costs of being unable to evaluate other (possibly even more promising) treatments because of limited money, patients, and clinical research centres with the capacity to conduct acute SCI trials. Additionally, while individuals with SCI who participate in an early (phase I or IIa) experimental trial might acknowledge that the trial's focus is to confirm the safety of the therapy being tested, it is understandable that they invariably hope that it will be of some benefit to them [49]. It is therefore the responsibility of the research community to ensure that the decision to move a treatment forward into clinical trials is based on careful consideration of its supporting preclinical evidence in experimental animal models [24].

25.3 Animal Models of SCI

Animal models allow for the controlled and rigorous study of injury responses and recovery. The animal cohorts can be relatively homogenous, the injury characteristics and conditions can be precisely controlled, and – compared to human clinical trials – the experiments are relatively inexpensive. In addition to tightly controlled experimental conditions, animal models offer the obvious advantage of being able to harvest the injured spinal cord itself from the euthanized animal for a myriad of different analyses (e.g. histology, biochemistry, molecular biology). It is important to recognize that the same factors that are often touted as advantages of animal model studies – tightly controlled conditions, homogeneous cohorts, precisely delivered mechanical injuries – also make such experiments quite distinct from clinical reality. In the latter, there is considerable heterogeneity and variability in baseline health, injury biomechanics, and subsequent treatment. This is a typically under-appreciated limitation of experimental paradigms that employ animal models for SCI research.

25.3.1 Injury Models

Contusion Models The majority of traumatic SCIs are caused by blunt trauma related to motor vehicle accidents (43 %), falls (18.8 %), and sporting injuries (11.1 %). These involve a sudden contusive force being applied to the spinal cord as the surrounding bony/ligamentous spinal column fails [75]. Penetrating trauma to the spinal cord from gunshot wounds or knife injuries is relatively uncommon in Western societies (see chapter 1).

The earliest forms of SCI modelling involved a replication of this contusive form of injury. The first documented animal model of SCI was described in 1911 by Alfred Reginald Allen [3]. In this canine SCI model, a 30 g mass was dropped from an 11 cm height along a rod, onto the dorsal surface of the exposed spinal cord. Generally speaking, the contusion injury models currently utilized are modifications of the original Allen injury model [100]. The first widely used weight-drop

SCI contusion device in rodents was the New York University impactor [35]. Injury severity with the NYU impactor is adjusted by altering the height from which a 10 g rod is dropped onto the exposed thoracic spinal cord: 6.25 mm (mild), 12.5 mm (moderate), 25 mm (severe), and 50 mm (very severe). The rod velocity is monitored to allow for validation and standardization of the injury mechanics. The NYU impactor was used in the 'multicenter animal spinal cord injury study' or 'MASCIS' and is often referred to now as the NYU-MASCIS or MASCIS impactor.

The NYU impactor was followed by the development of an electromagnetic impactor device by the Ohio State University (OSU) Spinal Cord Research Center. This device was computer controlled to precisely deliver a defined displacement to the dorsal thoracic spinal cord surface [11, 16, 43, 91]. The OSU electromagnetic SCI device (ESCID) was originally designed for use with rats but was also modified to be applicable in mice as well [43]. It has also been used to model cervical spinal cord injuries [61]. The computer control allows for the adjustment of displacement and velocity and provides feedback on the maximal impact force delivered.

In 2003, Scheff et al. reported on the ability of a new device, the infinite horizon (IH) impactor, to produce graded morphological and behavioural changes in a rodent model following contusion injury to the spinal cord at T10 [84]. To control the injury severity with the IH impactor, the impact force (kdyne) is adjusted; this is in contrast to the NYU-MASCIS impactor and OSU impactor in which the injury severity is adjusted by height of weight drop (and conversely velocity) or depth of tissue displacement (mm), respectively. The impactor has been modified to induce unilateral cervical spinal cord injuries [62] and can also be modified for use in smaller rodents such as mice by replacing the impacting tip with a smaller version [14]. A technical challenge with the IH impactor is in grasping the spinal column securely with its clamps. Streijger et al. recently reported on a design for a custom clamping system to improve upon this [93]. Like the NYU-MASCIS impactor, these contusive models are able to create graded injuries within the spinal cord and are characterized by central haemorrhagic necrosis, ischaemia and inflammation [12].

Clip-Compression Models In 1978, Rivlin and Tator developed the 'clip-compression' model of SCI in rats, in which the spinal cord was compressed dorsoventrally between the arms of a modified aneurysm clip [83]. The clips can be calibrated to exert a specific force to the spinal cord and induce graded injury severities [80]. This model demonstrated the relationship between the severity of neurologic injury and the severity and duration of compression. The Rivlin-Tator aneurysm clip was originally designed for use in the thoracic cord [83]. Recently, Fehlings and colleagues have developed modified protocols for its use at the C6–C7 and C7–T1 spinal levels [28].

The clip-compression model aims to replicate the effect of persistent spinal cord compression that is commonly found in clinical SCI. Compression, however, is typically applied for 1 min, which is vastly different from the duration of persistent compression that is witnessed in human SCI. The clip-compression and contusion

injuries both impart a blunt force to the spinal cord. They differ in that clip-compression injury lacks the initial velocity of the contusion injury, while contusion injuries do not impart the sustained spinal cord compression observed in human SCI. Even for commercially available contusion impactors, the velocity with which the spinal cord is impacted is considerably lower than what is estimated to occur in human SCI [77, 104].

Balloon-Induced Compression Models Tarlov first proposed the balloon-induced compression injury model in 1953 [96]. The model was developed due to its simplicity and non-invasive nature. Initially, a small hemilaminectomy defect was created to access the epidural space, into which a Fogarty catheter was inserted and advanced cranially to one or two higher spinal levels [67]. Alternatively, the catheter may be installed in the lumbosacral spine and advanced through the epidural space to the thoracic spinal cord. Inflating the balloon at the catheter tip with saline imparts the compressive force against the spinal cord [59]. Again, the injury can be graded using varied volumes within the balloon. This method of injury has been used in a variety of large animal species, including canines and monkeys [36, 59].

Transection Models While full transections are rare in the clinical setting [78, 94], the transection models offer the advantages of investigating axonal regeneration/plasticity, degeneration, tissue engineering strategies and cell transplantation [12]. Transections can be either complete or incomplete, with the latter intended to precisely interrupt specific tracts [18, 90]. For example, a dorsal hemisection can be used for selective transection of the corticospinal tracts, while a dorsolateral quadrant lesion can be used to transect the rubrospinal tract [12, 94]. The key advantage to transection models (either full or partial) is the more clear interpretation of axonal regeneration studies.

Photochemical Models A photochemical-based model of SCI was first developed in 1986 [101] and has been used as a method of creating a discrete SCI without significant primary trauma [30]. A dye is infused systemically and then activated within a discrete area of the spinal cord using an argon laser. The resultant photochemical reaction produces single oxygen molecules on the endothelial surface of spinal cord vessels, which triggers an aggressive platelet response, vessel occlusion, and damage to the parenchymal tissue [37]. The model is considered reliable and reproducible and does not require a full laminectomy. While this model is quite distinct from the high-energy injury models that resemble human injury, it can be useful for studying features of the secondary injury phase in the absence of significant mechanical trauma.

Excitotoxic Models Injury in the excitotoxic model is induced by an intraspinal or intrathecal injection of excitotoxins such as quisqualic acid, an α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-metabotropic receptor agonist [106]. These excitotoxins are particularly useful for generating rodent models of neuropathic pain with thermal hyperalgesia and mechanical allodynia [64, 71].

25.3.2 Animal Species Used in Modelling SCI

In addition to the variety of injury mechanisms used to induce SCI, there are numerous animal species that are used for SCI research. Rats and mice are by far the most commonly used animals for in vivo SCI modelling and experimentation [7, 33]. Other experimental species used for SCI research include gerbils, guinea pigs, hamsters, cats, dogs, pigs, and non-human primates [17, 42, 60, 67, 72, 76, 86, 108]. Other models include invertebrates such as eels [94], whose unique regenerative capacities have been investigated in an effort to understand the regenerative processes and how they might be harnessed in humans. While there is a breadth of animal species available for SCI modelling, one should recognize that each has its own advantages and disadvantages, and none necessarily represent the human condition with perfect biofidelity.

Rat Rat models are the most commonly used for SCI experimentation, and most SCI models were initially described and characterized in the rat [15, 27, 84, 91, 95, 105, 107]. They are relatively inexpensive, easy to handle and care for, and have long-established injury mechanisms available (e.g. contusion, clip compression, transection). They have well-described neuroanatomy, and there exists a wide array of behavioural tools as outcome measures. Locomotor recovery is typically evaluated with the widely used Basso, Beattie, and Bresnahan (BBB) scale, which has the advantage of being relatively inexpensive and comparable across laboratories [9]. More sophisticated systems for testing locomotor recovery have been established and are commercially available (e.g. catwalk) [99, 107]. While traditionally the rodent SCI models involved a mid- or low-thoracic injury and an assessment of lower limb recovery, a number of groups have developed methods for injuring the cervical spinal cord to specifically evaluate forelimb responses [40, 63, 69, 70, 85, 103].

Mouse Mouse models of SCI have the significant advantage of enabling the application of sophisticated genetic/molecular techniques to investigate the role of specific genetic factors that may influence biological responses to injury (e.g. cell death or axonal regeneration). The ability to enhance or delete specific genes allows for the study of their roles in gain of function and loss of function experiments. Using mice with a specific gene deletion has become a standard approach in SCI research, and Cre-lox technology along with increasing numbers of transgenic mice has provided greater spatiotemporal control of the knockout strategy and a better understanding on specific factors that affect axonal outgrowth. The small size of mice, however, makes surgical procedures more difficult and prohibits many device implantations [71, 94]. Similar to rats, investigators have modified the traditional thoracic SCI approaches to study cervical SCI in mice [1, 47, 92].

Cat The cat has been used extensively in locomotor studies that have contributed to a greater understanding of spinal networks controlling and regulating locomotor activity. The larger size of cats allows for a wider range of surgical implementation and the opportunity to execute detailed kinematic analyses in locomotor and pos-

tural studies. Anatomically, the spinal cord of cats is organized similarly to humans – specifically, the main part of the corticospinal tract is located in the dorsolateral spinal cord, while in rodents it is located below the dorsal columns. In the early twentieth century, the demonstration that the spinal cord could generate the basic rhythm of locomotion by itself was first shown in an adult cat model of SCI [19]. The cat SCI model has served as the foundation for seminal insights into locomotor training by researchers such as Serge Rossignol [6], Reggie Edgerton [68], and Susan Harkema [38]. The evidence of an intrinsic spinal locomotor network that can be activated using different types of stimulation was important for the development of rehabilitation strategies for spinal cord injured humans.

Dog Within the last two decades, rodent models of SCI have largely replaced the use of dogs in experimental SCI research. However, there has been increasing interest in 'naturally occurring' SCI that occurs in domestic dogs [44]. Dogs naturally suffer spinal cord injuries as the result of traffic accidents, or – in some species – acute thoracolumbar disc herniations [66]. Because of this, the mechanisms of injury are often similar to human SCI: vertebral fracture-luxation and disc extrusions, which both produce a combination contusion-compression lesion to the ventral aspect of the cord – something that is difficult to model experimentally [44]. The paradigm of a 'naturally occurring' SCI (in contrast to an experimentally induced SCI) lends itself to the conduct of a true 'clinical trial' that resembles how human trials are conducted [34]. Essentially, the clinical population of domestic dogs with SCI forms a 'surrogate human' population of clinical patients in which to test the efficacy of potential treatments for SCI. Recently, a population of spinal cord injured dogs was used in a prospective randomized clinical trial of an intraspinal transplantation of glial cells derived from the olfactory mucosa [34]. This study demonstrates the potential utility of this naturally occurring SCI in dogs to conduct a clinical trial of a novel therapeutic much in the same way as it would be conducted in humans.

Pig The pig has the spinal cord and CSF dimensions that are more similar than rodents to those of an adult human [60]. The obvious differences in size and anatomy and potentially greater similarities in biological responses to injury between humans and higher-order animals make a porcine model of SCI a useful model for the investigation of biological and cellular transplantation studies [60]. Additionally, while the costs associated with conducting studies in large animals are certainly higher than those with rodents, they are a fraction of those associated with primate studies. A number of investigators have described the development of pig models of SCI using a weight-drop impactor, computer-controlled contusion/compression devices, or calibrated vascular clips [60, 72, 108]. Using a weight-drop contusion device, Lee et al. developed a porcine model of traumatic thoracic SCI in Yucatan miniature pigs, where varying degrees of injury severity can be induced by altering the height (5, 10, 20, 30, 40, and 50 cm) from which a 50 g weight is dropped onto the dorsal aspect of the T10/T11 segment [60]. Locomotor recovery was evaluated using their Porcine Thoracic Injury Behaviour Scale (PTIBS), which was sensitive

at distinguishing recovery amongst animals of different injury severities [60]. Using a computer-controlled system, Navarro et al. developed a chronic SCI model in adult Gottingen-Minnesota pigs, where they showed consistent development of paraplegia following a 2.5 kg compression force, delivered at a velocity of 3 cm/s on the dorsal aspect of the T12 segment [72]. Zurita et al. developed a vascular clip model of SCI in adult minipigs, where paralysis was caused by the epidural application of two vascular clips for 30 min [108].

Non-human primate Non-human primate studies are primarily limited by their specialized facility requirements and high cost related to the intensity of animal care. Some also have ethical objections to their use. Nevertheless, their 'relatedness' to humans has made them an appealing species to preclinically evaluate novel therapies and has motivated researchers to develop injury models in them. In 2012, Nout et al. reported on a lateral hemisection model of cervical SCI in adult rhesus monkeys [76]. A lateral hemisection allows for precise control over the lesion location and extent, and it allows for some preservation of function in experimental animals so that the injury morbidity is reduced. A cervical contusion model of SCI in marmosets was developed by Iwanami et al., where a 17 g weight is dropped from a height of 50 mm onto the exposed dura matter of the C5 segment [42].

One of the main advantages of a cervical SCI model is the similarity in upper extremity function between humans and non-human primates. As regaining hand function is the highest priority for tetraplegic individuals [4], evaluating therapies in a primate cervical SCI model that influences the recovery of hand function is of translational importance [76]. Demonstrating the restoration of hand function in a primate model of cervical SCI is an important consideration for the translation of invasive and inherently risky cell transplantation therapies.

25.3.3 Limitations of Preclinical Experimentation Using Animal Models

While much effort has been made to refine various animal models in different injury species, it is worth at least acknowledging some of the broad limitations of the experimentation paradigms utilized in preclinical studies. As mentioned earlier, human SCI is incredibly heterogeneous in its causes, consequences, and pathology. Conversely, in animal studies, researchers typically endeavour to minimize experimental variability in as many ways as possible. Animals of the same weight, age, gender, and, sometimes, genetic background are accrued for an experiment, then subjected to a precise biomechanical injury (which imperfectly simulates the high velocity with which human injury occurs), and subsequently housed in identical post-injury conditions.

Additionally, conditions inherent to the experiment may influence the outcome. Anaesthesia, for example, is essential for the experiment but may by itself has neuroprotective effects. Pentobarbital and isoflurane, commonly used anaesthetics for

SCI experiments, have been shown to reduce infarct volume following ischaemia [39, 41, 46]. The general anaesthetic, ketamine, has been shown to reduce functional and histopathological indices of injury in gerbils subjected to cerebral ischaemia [39]. While there is no alternative to appropriately anaesthetizing the animals in experimental injury models, the potential effects of these drugs (albeit distributed equally across an experiment) need to be acknowledged.

It should also be acknowledged that the functional outcomes and behavioural assessments differ from experimental models and the clinical setting. Much effort has gone into the design of assessment scales and procedures that accurately measure functional recovery in animals. Some of the most commonly used tests in SCI research include the BBB scale [8], the Tarlov open-field test [96], and the inclined plane test [83]. Both the Tarlov and inclined plane tests assess general locomotor ability and do not reflect specific changes in motor or sensory function [48]. Alternatively, the BBB scale emphasizes hind limb function and does not assess other movements, which require coordinated spinal cord activity [2]. In the end, despite the refinements and widespread use of such outcome measures, the reality is that these measures have no physiologic correlate in humans. For example, it is impossible to predict how the achievement of 'plantar weight-supported stepping' on the BBB scale would translate into human lower extremity function. Researchers are warned to resist the temptation to extrapolate such changes in animal behaviour to human locomotor recovery.

Finally, the SCI field has become increasingly aware of the challenge of demonstrating the robustness of its novel therapies, as manifested by the difficulty in independently reproducing promising experimental findings (see chapter 20 and 21). This has, to some extent, been recognized for decades in many areas of biomedical research [22, 23, 88]. Recently, the biotechnology industry has reported on the difficulty of replicating many promising findings published in peer-reviewed journals [10, 79]. Poor study design and reporting practices in SCI research have likely resulted in biased results, considerable waste, and arguably, a slowing of progress towards developing effective therapeutics [65]. In the SCI field, a formal replication initiative funded by the National Institute of Neurological Disorders and Stroke (NINDS) resulted in the failure of the majority of promising SCI therapies [89]. Factors like litter-to-litter variability can impact behavioural studies significantly [58]. Concerns have also been raised regarding a number of issues in neuroscience publications, including inappropriate statistics [20, 73], low power [21], and a need to decrease p values from 0.05 to 0.005–0.001 [45]. Recently there has been support for implementing reporting standards for preclinical research that are analogous to the reporting of clinical trials, as the absence of such standards may influence the interpretation of study results [65]. For example, RhoA/Rock inhibitor and stem cell studies for SCI treatment have been shown to describe more favourable outcomes when the articles do not report whether investigators were blinded during behavioural testing [5, 102]. Efforts such as these will improve the quality of SCI research and help the field interpret the overwhelming body of literature that is emerging on novel therapeutics.

25.4 What Constitutes 'Enough' Preclinical Evidence to Proceed with Human Trials?

The experience of testing promising experimental therapies in clinical trials of SCI has taught the field much about the challenges associated with successfully translating such novel technologies into clinically efficacious treatments for human patients. These experiences have led to important initiatives to identify the obstacles and challenges to successful translation and potentially improve upon the chances of succeeding in future trials [25, 56, 87, 98]. Such initiatives span the continuum from recommendations around preclinical laboratory studies to the planning and conduct of clinical trials.

One area of specific interest within this continuum is the issue of determining what preclinical evidence is needed to justify moving a promising experimental therapy towards a lengthy and expensive human clinical trial [13, 24]: *When demonstrating a therapy's efficacy*, *what animal model is sufficient*? *What is the most relevant injury model of human SCI*? *What constitutes* '*clinically meaningful efficacy*?' *How much scientific evidence that a cellular therapy* '*works*' *in preclinical models of SCI is enough before proceeding with a human clinical trial*? These are complex questions which do not currently have straightforward answers, as we do not have the luxury of looking back retrospectively at how clinically efficacious therapies for SCI were evaluated preclinically prior to human testing. On one hand, the devastating effects of SCI and the untreatable nature of the neurologic impairment provide good reasons to aggressively move therapies forward that appear promising, particularly if they have an acceptable safety profile. On the other hand, the time and money required to complete a clinical trial and the potential risks associated with some therapies such as cellular transplantation provide good reason to 'thoroughly investigate and establish the robustness' of a promising therapy in preclinical studies.

We have undertaken a series of initiatives to characterize the perspectives of various stakeholders on this issue and provide the field with some guidance around these translational considerations [49–51, 53–55]. We first conducted a survey of the research community about what they felt was needed to translate a novel therapy to human clinical trials [51]. This survey was completed by over 300 respondents and provided a wide breadth of opinions from scientists, clinicians, and trainees. The results of this survey revealed a number of interesting perspectives around translation. There was strong support for testing therapies and demonstrating efficacy in multiple animal species (in addition to rodents) before human clinical trials. Particularly for invasive cell transplantation strategies, the majority advocated for large animal and primate model testing prior to human trials. The majority of respondents favoured contusion injuries over compression injuries as being the most clinically relevant mechanism of injury. Respondents were also keen to see therapies preclinically tested in relevant post-injury time windows, recognizing that there is an inevitable delay in administering treatments in the human setting. There was nearly universal support for the need for independent replication.

This initial survey captured opinions from the research community, and we extended this to garner the perspectives of individuals living with SCI [49]. Recognizing that SCI individuals do not have the same scientific background as researchers, the questions were analogous to our initial survey but asked in a slightly different manner. Instead of asking a question such as 'should the efficacy of a neuroprotective drug be demonstrated by independent laboratories in replication studies?' we posed it as 'if you were being offered a neuroprotective drug as part of a clinical trial, would you expect that its effectiveness had been demonstrated in the laboratory by multiple independent researchers?'. The results of this survey of over 200 individuals living with SCI suggested that they were more likely than SCI researchers to agree that preclinical safety and efficacy data in small animal models (e.g. rats or mice) represented sufficient evidence to proceed with clinical trials for both non-invasive neuroprotective drug therapies and invasive stem cell therapies. However, despite this sentiment, the majority of individuals with SCI still expressed the opinion that demonstrating efficacy and assuring safety of drug and cell therapies in large animal models and primates were needed. Over 80 % of individuals with SCI agreed that independent replication of the efficacy of promising therapies was needed prior to initiating human trials. The data supports the contention that individuals with SCI expect high levels of preclinical robustness before experimental therapies are offered to them in clinical trials, a sentiment that is also shared by the majority of the research community. In essence, we found that while individuals living with SCI are desperate for effective therapies, they have high expectations of the research community to 'prove' that they are effective prior to human testing.

The perspectives from the survey of the SCI researchers were used in conjunction with a modified Delphi consensus-building process to establish an objective grading scale for evaluating the preclinical literature on experimental therapies [53]. While there might be a series of peer-reviewed papers describing the testing of a specific treatment in animal models of SCI, there is currently no methodology for compiling that body of literature in an objective manner to assess how 'ready' the therapy is for human translation. This initiative attempted to address this issue. Here, we used the general considerations that emerged from our initial surveys of the research community: animal species, injury models/mechanisms, time windows, the extent of clinically meaningful efficacy demonstrated, and independent replication. A focus group of SCI research experts was assembled, and a grading scale was established to take into consideration the extent to which a non-invasive neuroprotective therapy had been preclinically evaluated [52]. For example, the score given to a study, based on the animal model used to demonstrate efficacy, was 2, 4, 6, or 8 points for a mouse, rat, large animal, or primate model of traumatic SCI, respectively. Alternatively, negative scores were applied with a negative independent replication study.

The opinions of clinicians and scientists also provided important guidance about how to consider preclinical efficacy in other acute or chronic neurologic conditions (e.g. stroke, traumatic brain injury, Parkinson's, multiple sclerosis, amyotrophic lateral sclerosis). The initiative asked participants to consider what 'clinically meaningful efficacy' actually entails in our preclinical studies. A myriad of behavioural and

nonbehavioural outcome measures are used to report the results of experimental treatments in preclinical animal SCI studies. These include such measures as locomotor recovery (e.g. BBB scores, catwalk, ladder footfall testing), non-motor recovery (e.g. mechanical allodynia), and histological/anatomical changes (e.g. lesion size, white matter sparing) [53]. While there is great importance in the demonstration of both behavioural and nonbehavioural improvements, there was general agreement that one would not favour translation of a treatment into humans solely on the basis of histological findings and in the absence of some demonstrable functional benefit. Additionally, a treatment with only a behavioural effect (e.g. improved hind limb function) but no associated improvement in any nonbehavioural outcome measure (e.g. tissue sparing, axonal sprouting) would be viewed as being premature for translation.

The scoring system that was developed, in essence, attempts to reflect how extensively a particular therapy has been studied, and any given treatment logically accrues points and a higher score as the body of peer-reviewed literature on it incrementally grows. The grading system attempts not only to identify which types of studies are important in the preclinical development of a therapy but also to provide perspective on how many have actually been done. On this 100-point scale, a therapy would accumulate points if it had been tested and shown to be efficacious in both small and large animal/primate models, in multiple injury mechanisms, with clinically relevant time windows of intervention, and by multiple independent laboratories. Using a systematic review of the literature on such neuroprotective agents [52], this initiative revealed that while the agents in current clinical trial were the therapies that scored the highest on this preclinical rating scale, the scores were still less than 50 – suggesting that many desirable aspects of preclinical testing had not been performed prior to the initiation of human trials.

Given the explosion of interest in stem cell transplantation, we conducted a subsequent initiative to assemble experts in the cell transplantation field to provide perspectives on specific questions related to ‘how much preclinical study is enough’ for cell therapies [54]. This initiative mirrored our initial survey but was restricted to researchers doing cell transplantation research and sought to address considerations that were unique to the translation of invasive cell technologies.

One issue that has plagued the community is the question of how long of a post-injury transplantation interval there should be in animal studies to simulate the ‘chronically injured’ SCI individual undergoing a cell transplantation procedure at least 18 months post-injury. Most participants felt that a delay of intervention of at least 3 months was warranted in preclinical studies. Fewer than 20 % of respondents felt that 6 weeks was a sufficient delay. However, for clinical trial enrolment in the 1–6-month range, a 6-week delay in transplantation in preclinical studies received more support. Perhaps most informative was the fact that no respondent felt that it would be justified to transplant a cell therapy into an individual with a chronic SCI if the cell’s efficacy had been demonstrated only at 7–14 days post-injury in a preclinical study. Discounting the results of a replication study due to a failure to reproduce all of the exact experimental conditions of the index study may be scientifically justified. However, we do this at our own peril, as this rationalization overlooks the

reality that human SCI occurs with variability that far exceeds the typical experimental conditions [74].

More recently, we continued this approach of utilizing a targeted questionnaire and focus-group meeting to address the role of large animal and primate models in SCI research [55]. This was intended to explore in more detail some of the perspectives that arose from our previous surveys about the need for testing therapies in animal species beyond rodents. For example, *if large animal and primate models are available for the testing of drug or cell therapies*, *what specifically should they be used to demonstrate*? *Are they both needed*? *How should efficacy or failure in such models be interpreted and acted upon*? *How much rodent work is needed before it makes sense to move into large animal or primate testing*? This initiative involved 41 individuals from academia, the biotechnology industry, and granting agencies, with an effort to broaden the perspectives.

In general, the importance of using large animal models and primate models in preclinical SCI research was reaffirmed, although it was clear that the participants felt that demonstrating efficacy in these models should not be an FDA requirement for moving to clinical trials. Despite this, many felt that the failure to demonstrate the efficacy of drugs or cells in large animal or primate models was sufficient reason to *not* proceed with human translation. Also, most participants advocated for at least an independent replication of efficacy in rodent models before taking a therapy forward into much more expensive testing in large animals or primates.

While this effort addressed specific considerations around the use of large animal and primate models of SCI, it is also worth noting that the assumption that large animal and primate models are somehow 'better' than rodent models and more predictive of success in human clinical trials has not yet been tested. Indeed, the characteristics of any animal model that specifically predicts successful translation into human SCI have not been identified. Overall, the sentiment is generally shared that if an experimental therapy can promote neurologic recovery in a rodent injury model and then similar efficacy in a large animal (e.g. pig) and/or non-human primate model is shown, then its likelihood of 'working' in human SCI is greater. In essence, such a demonstration would be interpreted as a greater 'robustness' of the therapy, although this interpretation has yet to be substantiated.

25.5 Summary

Animal models will continue to be a cornerstone of discovery and validation for SCI. The emergence of increasing numbers of potential therapies will demand vigilance at the preclinical level to demonstrate the robustness of effect and put forth the most promising candidates, lest we overwhelm the clinical community with treatments destined to fail. The wide range of animal models and animal species that are now available give the scientific community new opportunities to address important translational questions prior to human testing. The future challenge will be in balancing the urgent needs of the injured community for effective therapies with the

hesitation to put things into clinical trial without 'sufficient' testing. Ongoing dialogue that involves scientists, clinicians, regulatory agencies, funding agencies, and individuals living with SCI is imperative to ensure that this balance is struck in such a way that we move forward efficiently towards the establishment of effective therapies.

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Clinical Trials and Spinal Cord Injury: Challenges and Therapeutic Interventions

26

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Abstract

In SCI, like other diseases, randomized control trials (RCTs) represent the gold standard towards establishing the efficacy of novel treatments. RCTs in SCI present with their own unique set of challenges, including considerable injury heterogeneity, low numbers, variable outcome measures, and ethical concerns. Many of these challenges are compounded by difficulties in translation between animal models and the real human condition. As a consequence, current treatments to improve neurological outcomes after SCI remain limited. In this chapter, we detail many of the challenges of conducting RCTs in SCI, whilst exploring progress of several potential therapies to protect and repair nervous system tissue in humans.

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26.1 Overview: Basic Premise of Acute Interventions to Improve Neurological Outcomes for Individuals with SCI

In an attempt to overcome the limited capacity for regeneration in the central nervous system (CNS), acute therapeutic interventions generally fall into one of two categories: neuroprotection and neural regeneration. Following primary damage to the spinal cord, a cascade of biochemical events triggers secondary injury to spared white and grey matter (see chapter 19). Towards preventing the cascade of secondary injury mechanisms, a window of opportunity for neuroprotection is thought to emerge in the initial hours to days after injury [51]. While preventing secondary injury represents a reasonable target for improving neurological outcomes, full restoration of sensory and motor function requires regeneration in the spinal cord [54]. Emerging regenerative therapies are focused on promoting functional recovery by inhibiting factors that prevent endogenous repair or biochemicals that promote axonal sprouting (e.g. short-distance growth) [23]. The goal of this chapter is to provide an overview of studies supporting acute neuroprotective and regenerative interventions as effective strategies to enhance neurological outcomes after spinal cord injury (SCI).

26.2 Challenges of Spinal Cord Injury Trials

Before reviewing interventions conducted in the field of SCI, it is important to briefly describe the challenges facing researchers and clinicians performing clinical trials. While not necessarily unique to SCI, these challenges represent a significant barrier to detecting therapeutic benefits of any intervention and linking neurological improvements with long-term functional benefits.

26.2.1 A 'Moving Target': Effect of Spontaneous Neurological Recovery

SCI is a devastating neurological condition, often characterized by severe and lifelong impairments. Similar to other traumatic neurological conditions (e.g. stroke), SCI is associated with some degree of neurological and functional recovery. Neurological recovery is most evident in the initial days to weeks post-injury and is characterized by a rapid increase in muscle strength for up to 6–9 months and generally plateauing by 1 year [14, 41, 56, 66]. Neurological recovery is best predicted by the initial severity of damage in the spinal cord, as individuals with less severe injuries are capable of greater recovery than individuals with more severe injuries [14]. Neurological recovery is fundamental to the return of functional independence, such as self-care and ambulation. In terms of designing clinical trials, the benefits of a therapeutic intervention must be distinguishable from naturally occurring recovery of function. Moreover, it requires careful consideration in terms of study design, ensuring that injury severities are equally distributed between treatment arms of a clinical trial [55]. This can be problematic and is related to our second challenge: low numbers of suitable patients.

26.2.2 Low Numbers: SCI as an 'Orphan' Disease

Thankfully, SCI is not a common neurological condition and is recognized in Europe and the United States as an 'orphan' disease. While providing incentive for industry partners to target SCI (e.g. extended patent protection), the low incidence of acute SCI makes performing a clinical trial very challenging. High heterogeneity in injury severity leads to variable neurological recovery profiles, further exacerbating this problem [55]. This, in addition to other factors, prevents individuals with SCI from being eligible to participate in trials and creates a 'funnel effect' in which a large number of potentially eligible participants are significantly reduced by inclusion/exclusion criteria. As an example, 1,816 patients were prescreened for a recent phase 2 multicentre study examining the acute neurological effects of autologous cellular therapy in individuals with SCI [35]. After excluding subjects for being more than 14 days post-injury, having the incorrect injury characteristics and/or failing to meet MRI criteria, the final recruitment number was 50. Of these 50 individuals, only 32 completed the follow-up assessment at 12 months [35].

26.2.3 Enrolment and Assessment into an Acute Clinical Trial: Very Early Interventions May Be Necessary

Low subject numbers for clinical trials are particularly problematic for neuroprotective strategies, which necessitate very acute interventions (i.e. initial hours after SCI). Several practical constraints limit recruitment, including patient transportation to a participating centre, acquiring informed consent and confirming that a participant meets all inclusion criteria. Substantial barriers exist for each of these requirements, including ethical debates as to whether an individual with acute SCI can reasonably be expected to provide informed consent (see Sect. 26.2.5 below). Of paramount importance, detecting efficacy of an acute intervention is contingent on the validity and reliability of the acute neurological assessment. This is important both in terms of enrolling the correct subjects and establishing baseline measurements that will serve as anchors from which to measure change. In practice, an accurate (i.e. reliable) neurological exam may be very difficult to perform in patients with very acute SCI (<72 h), related to spinal shock, co-concomitant injuries, ventilator use or the influence of drugs or alcohol in the very early stages [18].

26.2.4 Neurological Outcome Measures: What Is the Best Outcome to Assess Efficacy?

As already described, an accurate neurological examination soon after injury is integral for assessing subsequent neurological recovery. Equally important, neurological outcomes need to be sensitive to subtle changes, yet representative of important changes in function. The selection of different neurological outcomes may vary depending on the phase of study and range from neurophysiological, e.g. somatosensory evoked potentials (SSEPs), to a more conventional examination of muscle strength and sensory function (i.e. the International Standards for

the Neurological Classification of Spinal Cord Injury (ISNCSCI)) [55]. The incorporation of neurophysiological tools is important for detecting subtle changes in neurology, which may go undetected according to other, more subjective measures. Neurophysiology may also play an important role in early phases of study, supporting a potential mechanism and substrate for neurological repair and regeneration (e.g. decreased latencies of SSEPs as an indication of remyelination (see chapter 11)). Several outcomes can be derived from the ISNCSCI and have been used to measure efficacy of acute therapeutics, including changes in total motor score (i.e. upper and lower extremities), and the American Spinal Injury Association Impairment Scale (AIS) grade conversion [55]. Changes in motor levels also have been proposed as a viable clinical trial endpoint among individuals with tetraplegia. Motor level recovery may be particularly important among individuals with cervical sensorimotor complete injuries, where recovery of segmental muscle strength near the injury site may precipitate significant improvement in hand function [41]. Several prominent issues with the ISNCSCI remain for applications in clinical trials. For example, information regarding the extent of neurological improvement that is considered 'minimally clinically important' is lacking [64]. This complex issue requires delicate weighting of potential benefits of neurological improvements with functional outcomes, as well as an analysis of the potential cost to the individual (i.e. side effects).

26.2.5 Ethical Issues: Informed Consent and Potential Risks

There is an ongoing debate as to whether an individual sustaining an acute SCI can provide informed consent to participate in a clinical trial [17]. This is a barrier to recruitment and worthy of serious consideration. Ethical issues around this topic stem from the capacity of acutely injured individuals to make decisions and process the relevant information regarding potential risks, rewards and long-term implications (e.g. potential to be excluded from other clinical trials) and therefore knowledgably consent or decline participation [17]. Other ethical issues arise for invasive treatments in SCI (e.g. 'first-in-man' therapies) and trials where a true placebo arm might be unethical and/or introduce unnecessary risk or harm [35, 60]. There is a particular concern regarding the possibility that some cellular therapies may lead to tumour growth and that strategies promoting plasticity may lead to the development of neuropathic pain.

26.2.6 Translation from Animal Models to Humans with Spinal Cord Injury: What Is the Right Model?

Prior to application in human clinical trials, an intervention is required to have a demonstrated history of safety and efficacy in animal models of SCI (see chapter 25). Animal models of SCI have included a variety of experimental injuries (e.g. contusion or transection) in mice, rats, cats, dogs, swine and

non-human primates [54]. Despite substantial preclinical evidence of neurological improvements from neuroprotective or reparative therapeutic interventions, no treatment has transitioned successfully into humans (note: more on the specifics of failed clinical trials below). However, challenges emerge *within* animal studies, particularly with regard to the replication of preclinical results, even within the same species and/or similar model conditions [50, 52]. This lack of reproducibility in seemingly identical animal models can occur for a variety of experimental and biological reasons [52]. The assessment of functional recovery within and across species can vary widely, and even commonly accepted measures (such as the Basso, Beattie, and Bresnahan (BBB) scale for hindlimb recovery in rat models) may be improperly conducted or subjectively interpreted [24]. Other sources of variation across studies include lesion severity, strains of animal and behavioural influences (e.g. a stressful environment) [24]. These failures have led some investigators to suggest that animal models do not accurately predict whether a therapy will be effective in humans. However, the translational path to clinical studies is not 'smooth or well travelled'. Among suspected translation problems are the human condition being more heterogeneous than experimental SCI, differences in the natural history of recovery as well as the appropriate design of study protocols and outcome measures [16].

26.3 Past and Current Interventions in Spinal Cord Injury

Despite the numerous challenges, researchers and clinicians have embarked on several acute randomized clinical trials to improve long-term neurological outcomes after SCI (see also Chapter 20). Below we have provided a summary of several prominent investigations that have applied an acute neuroprotective or regenerative intervention in humans with SCI.

26.3.1 Neuroprotection

26.3.1.1 Surgical Decompression

Surgical decompression following SCI is performed to reduce pressure on the spinal cord and involves the removal of the bone as well as the instrumentation of the vertebrae to stabilize the spinal column and prevent further injury (see chapter 7) [51, 63]. Although successful in animal models, surgical decompression in humans has generated more variable outcomes. In terms of neurological recovery, retrospective studies have largely confirmed the safety of surgical decompression but provided limited evidence of efficacy [62]. An important caveat to safety is that postsurgical interventions may compromise spontaneous neurological recovery [53]. Prospective observational studies have found more encouraging evidence for surgical decompression after SCI. A recent multicentre study found that early (<24 h) surgery was associated with reduced length of stay in a hospital and greater neurological recovery compared to late decompression (>24 h) [21]. Neurological

recovery was defined in this study as an improvement by two AIS grades at 6 months post-injury. However, an important limitation of this study is that individuals were not randomized to early and late decompression. This obvious limitation means that other factors such as the severity of concomitant trauma along with SCI or longer time to stabilize a person for surgery may confound the benefits of acute surgical decompression. The only randomized clinical trial reported so far only demonstrated a significant effect on neurological recovery for very early decompressive surgery (<8 h) compared to very late (3–15 days) surgical intervention in a small (n = 27) patient study [11]. Nevertheless, based on these observations, surgical decompression now represents a standard of care for many individuals with acute SCI across many trauma centres in Canada, the United States, and Europe.

26.3.1.2 Therapeutic Hypothermia

Hypothermia has been proposed as a neuroprotective strategy based on a potential application to slow metabolism and thus reduce a variety of secondary injury mechanisms, including decreasing free radical generation, inhibiting excitotoxicity and apoptosis, ameliorating inflammation, preserving the blood-spinal cord barrier, inhibiting astrogliosis, promoting angiogenesis as well as decreasing axonal damage and encouraging neurogenesis [61]. In rats, systemic moderate hypothermia (32°C) initiated 2 h after an ischemic SCI improved behavioural outcomes and increased tissue sparing [48]. Similar behavioural and histological outcomes have been reported for contusion models of SCI, although hypothermia has been applied at considerably earlier time points (e.g. 5–30 min post-injury) [46, 65]. A systematic review of studies investigating the use of hypothermia in humans indicated that there have been encouraging results with regard to neurological recovery so far; however, this review only spanned five articles for a total of 70 people with SCI [1, 15]. A large, multicentre randomized clinical trial has yet to be performed for hypothermia.

26.3.1.3 Pharmacological Interventions

Methylprednisolone

The application of corticosteroids to reduce secondary inflammation represents the most extensively tested neuroprotective intervention examined to date for human SCI. Based on animal studies, corticosteroids (i.e. methylprednisolone [MP]) became widely used in humans to improve neurological outcomes after SCI. In the first multicentre double-blind randomized controlled trial (RCT), initiated in 1979, 330 patients with acute SCI were administered low and high doses of MP [4]. The study compared two different dosages with no control group and yielded no beneficial effect on neurological function at 6 or 12 months. Based on new data from animal models, indicating a requirement for even higher dosages to have a beneficial neurological effect, a second larger, prospective, placebo-controlled RCT was initiated. In response to MP administered within 8 h of injury, improved neurological function (i.e. sensory and motor scores according to the ISNCSCI) was observed compared to placebo [5]. The timing and dosages from this study were then adopted

as the 'standard of care' [9, 42, 54]. The National Acute Spinal Cord Injury Study (NASCIS) III randomized, double-blind, multicentre trial (n = 499) was then performed without placebo in order to refine the ideal duration of treatment [7]. They found that administering MP within 3–8 h after injury and continuing for 48 h improved motor function at 6 weeks and 6 months post-injury, though not at 1 year. The NASCIS studies used motor and sensory index scores as primary endpoints, and NASCIS III also incorporated a functional outcome (i.e. the Functional Independence Measure) [5–7]. These studies spurred other RCTs examining the effects of MP, which produced uncertain or mixed results, in addition to growing criticisms regarding the claims and methodologies (e.g. skewed groups, complex weighting scheme, post hoc analysis) of the original NASCIS studies. Also of major concern were the documented adverse effects of MP treatment, including immunological compromise, sepsis, pneumonia, gastrointestinal and pulmonary complications and myopathy [9, 42, 54]. As a result of these concerns, as well as a growing lack of evidence supporting efficacy, MP use in SCI began to fade [42, 51]. The three NASCIS studies included a total of 1242 participants [5–7]. Interestingly, for a time, MP was widely adopted as a treatment even though it was never approved by a regulatory agency as a treatment for acute SCI.

GM-1 Ganglioside (Sygen)

Monosialotetrahexosylganglioside (GM-1) is a naturally occurring ganglioside found in human cell membranes, believed to have neuroprotective and regenerative properties [27, 54]. A small (n = 37) double-blind pilot RCT, examining the effects of GM-1 on neurological recovery after acute SCI, reported a significant improvement in both the Frankel scale and the American Spinal Injury Association (ASIA) motor score with no associated adverse effects [28]. The safety and early success of this pilot study propelled a much larger phase III multicentre trial (n = 760), which began in 1992, and compared two dosages to a placebo control. A priori, a two-grade improvement from baseline in the Modified Benzel Scale (a scale similar to the AIS grades but with additional grades to more clearly identify improvements within the mildest severity of SCI) was chosen as the primary outcome measure. Six months after SCI was selected as the primary trial endpoint [27]. Despite the encouraging evidence from the pilot study, this larger RCT showed no significant difference between those treated with GM-1 and the placebo control group. Although the results were disappointing, the study introduced many important criteria to improve the rigour of human SCI studies, including a defined a priori endpoint, improved outcome definitions and ongoing assessment for the training and reliability of outcome examinations [42].

Autologous Activated Macrophages

The inflammatory and immune response by the damaged CNS includes a prominent mobilization of endogenous microglia and exogenous macrophages to the SCI site, which has been suggested to be a significant source of secondary damage and cell death. However, some experimental studies in animals have shown that autologous activated macrophages promote growth and healing, as opposed to harmful

inflammation [42, 54]. Based on preclinical evidence, involving the direct injection of autologous activated macrophages into the spinal cord, a small (n = 8) phase I non-randomized study was initiated in 2000. Marked neurological improvements were reported for the treatment group in terms of AIS grade conversion from A (i.e. sensorimotor complete) to C (i.e. sensory and motor incomplete) [38]. These results stimulated a multicentre phase III RCT 3 years later. Recruiting a total of 43 subjects, autologous activated macrophages failed to show significant improvements in the primary outcome measure (i.e. AIS grade conversion) within the treatment group at 6- and 12-month follow-up [43]. Although disappointing, this study represented a milestone for acute SCI: the first time a cell-based therapy had been administered after SCI [42].

Minocycline

Minocycline is a broad-spectrum antibiotic that has been investigated for its potential to decrease inflammatory reactions following SCI [54, 63]. Although laboratory results have shown conflicting results with regard to its efficacy in animal models, a phase II placebo-controlled clinical trial was recently completed in Canada, administering minocycline within 12 h of injury [10, 54]. This study included 44 individuals with complete and incomplete SCI and confirmed the safety of minocycline use in humans, but did not show any significant neurological improvement compared with the placebo group. Although motor improvement in the treatment arm for incomplete SCI was greater than that of the placebo group, it remains within the range of plausible spontaneous neurological recovery outcomes [40]. The authors suggested that the low numbers in each treatment arm and the heterogeneity of the study groups warranted further research into the efficacy of minocycline after acute SCI [40].

Riluzole

Increased activation of voltage-gated sodium ion channels is thought to play a pivotal role in secondary cell death after SCI through a variety of secondary injury mechanisms (e.g. swelling, acidosis and glutaminergic excitotoxicity) (see chapter 19) [19]. Based on this information, riluzole, a sodium channel blocker, has been proposed as a pharmacological intervention to modulate concentrations of glutamate, thereby protecting the spinal cord from secondary damage [51, 54]. Currently administered for management of amyotrophic lateral sclerosis (ALS), riluzole is in the early stages of clinical trials in SCI [54]. A phase I safety trial administering an initial dose of riluzole (n = 36) within 12 h post-injury reported no increased risk of adverse events. Compared to historical controls, riluzole also had a small beneficial effect on motor outcomes and a tendency for greater AIS grade conversion [31]. A multicentre phase II trial is currently being conducted by the North American Clinical Trials Network (NACTN), as well as a multicentre phase II/III trial known as Riluzole in Spinal Cord Injury Study (RISCIS) [19, 22, 49, 63].

Gacyclidine

Gacyclidine is an *N-Methyl-D-aspartate* (NMDA) receptor antagonist and has demonstrated neuroprotective effects against glutamate excitotoxicity in rodents following SCI [58]. Gacyclidine was tested for safety and efficacy in a phase II randomized, placebo-controlled study in France initiated in 1995 ($n = 280$) [58]. Under community assent laws, where people with SCI were enrolled without informed consent, participants received their first injection of one of three possible dosages within 2 h post-injury. Primary outcome measures included the Functional Independence Measure (FIM) and motor, light touch and pinprick scores according to ISNCSCI. While there were no significant overall differences between groups for any of the neurological outcomes, a small group of cervical sensorimotor incomplete patients showed improvement. Thus, gacyclidine represents a notable achievement related to the very quick administration of a therapeutic after SCI [58]. It is interesting to ponder whether such an assent participation process in a trial could be undertaken today.

26.3.2 Regeneration and Repair

26.3.2.1 Cethrin

Inhibition of the Rho pathway results in the polymerization of actin, increasing axonal growth and neuroplasticity [20, 54, 63]. The Rho pathway can be inhibited using C3 transferase (i.e. Cethrin) and has shown improved functional outcomes in preclinical animal models [54]. A phase I/II multicentre study ($n = 48$) examined the safety of five different Cethrin doses with intrathecal application to the dorsal cord surface overlying the site of injury in patients undergoing surgical decompression [20]. In addition to establishing safety, modest improved motor recovery was suggested based on slight improvement in AIS motor scores [20]. However, a subsequent phase II/III randomized control trial was terminated before completion due to insufficient funds [54].

26.3.2.2 Cell Transplants

Stem, or more correctly progenitor, cells have been proposed to ameliorate lost sensory and motor function by replacing lost neurons or stimulating sprouting from preserved or transected axons in the spinal cord. The use of human embryonic stem cells (hESCs) in individuals with SCI was first approved in 2009; however, the trial ended prematurely with five of the eight participants receiving hESC-derived cell transplants [25, 51]. Though the termination of the trial was said to be due to financial reasons, it had already begun to receive criticism for having limited preclinical evidence, opting to use a SCI disease model, and choosing a population of subacute complete SCI patients [3, 8, 37, 51]. Among those individuals that underwent transplantation, no neurological improvement or serious adverse events were reported [33]. These five participants will continue to be followed for 15 years, potentially providing insight into the long-term safety and efficacy of stem cell intervention.

Induced pluripotent stem cells (iPSCs) have much of the same pluripotent ability as hESCs but are derived from adult tissues [2]. A preclinical study of transplanted human iPSC-derived cells into a non-human primate model found immunohistochemical results suggestive of increased axonal sparing/regrowth at the site of injury without tumour formation [39]. Currently, neural progenitor cell transplants have shown promising results for safety and functional improvement in animal models and have moved forward to a human clinical trial [2, 51, 54]. A phase I/II trial of human neural stem cells has recently been completed in Switzerland and Canada with 12 patients receiving human fetal-derived neural cell transplants into their spinal cord [51, 54].

Schwann cells myelinate axons in the peripheral nervous system (PNS) and promote axon regeneration and are therefore a molecule of interest in SCI regenerative studies [54]. The transplantation of Schwann cells at the location of injury has shown progress in laboratory and animal models and is also underway in human trials [51]. A phase I clinical trial ($n = 8$) has commenced in which an acute thoracic SCI patient's own Schwann cells are transplanted [2]. Other glial cells shown to promote axonal growth, currently being investigated in the field of SCI, are olfactory ensheathing cells (OEC) which, as the name implies, ensheath olfactory axons [51]. The transplantation of OECs was performed in a small ($n = 6$) phase I/II clinical trial in which no tumour or cyst formation developed, but no significant functional improvements were reported [47]. A separate phase I/II clinical trial ($n = 20$) found motor improvements in over half of the participants, with adverse events occurring in 5 or 20 patients [45].

26.3.2.3 Anti-Nogo

A wealth of evidence from preclinical animal studies suggests that neuroplasticity, as well as axonal regeneration in the CNS, is possible, though highly restricted by the presence of inhibitory molecules associated with adult CNS myelin and astrocytes [68]. Among promising targets to enhance regeneration and promote recovery, inhibition of myelin-associated protein Nogo-A by a specific antibody has been the focus of investigation [30, 67]. One study used 13 monkeys to examine the effect of anti-Nogo-A on manual dexterity following a unilateral cervical lesion. They found that the treatment group experienced significantly improved motor recovery with no reported adverse effects [26]. A phase I trial involving 52 patients with acute SCI has so far demonstrated the safety of anti-Nogo therapy, though full results have not yet been published, and a phase II trial has been planned [33, 51, 68].

26.4 Future Directions

Research has provided a wealth of knowledge regarding the biological processes following SCI and those involved in neural protection and regeneration. Although many barriers exist in the translation of treatments from 'bench to bedside', advancements are continually being made to improve this process. In 2006, the Spinal Cord Outcomes Partnership Endeavor (SCOPE) Steering Committee was founded. The

overall goals of SCOPE include facilitating communication between various disciplines involved in SCI interventions (e.g. researchers, clinicians, government agencies), fostering collaborations, identifying measurement tools, developing protocols and updating and disseminating current knowledge. Specifically, they have published guidelines for the conduct of clinical trials in SCI, as well as studies regarding the use of statistical power and outcome measures within these trials [18, 44, 57]. They have applied novel techniques to identify homogenous SCI subgroups in the prediction of future clinical outcomes [59]. Going forward, these SCOPE endeavours will be important in the development and harmonization of clinical trial protocols. Other areas of focus for the future of SCI clinical trials include the development of biomarkers and potentially repurposing existing medications for neurological benefit [12].

In addition to these improved regulations around clinical trials, research on SCI treatments is increasingly moving towards the investigation of combinatorial strategies to promote sensorimotor recovery [13, 34]. A recent systematic review of strategies to improve motor recovery after SCI in humans found that the highest level of evidence supported combinatorial approaches that included a rehabilitation component [29]. Unlike acute therapies after SCI, therapies in the chronic stage tend to focus more on regeneration (as opposed to neuroprotection) [36]. Although studies in chronic SCI face many of the same challenges as acute studies (e.g. low numbers, poor translation and meaningful outcomes measures), the lack of spontaneous recovery in this population can provide a stable baseline from which to measure benefits [64]. However, chronic interventions also face their own unique challenges, as chronic injuries demonstrate diminished regenerative capacities. For these reasons, therapies that show promise in acute populations are often not being applied or are not effective in the chronic population [32].

26.5 Summary

With the caveat that RCTs are still needed to confirm prospective, observational studies, only surgical decompression and activity-dependent rehabilitation represent current acute interventions thought to improve long-term neurological and functional outcomes for individuals with SCI. Despite emerging evidence in animal models, pharmacological interventions have yet to demonstrate efficacy in humans. Study failures may be attributable to several factors, including physiological differences between animal models and humans, low statistical power, variation across outcome measures, ethical considerations and heterogeneity of SCI [14, 16–18, 35, 40, 60].

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