Karen L. Roos
Editor

Emergency Neurology

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Preface

The evaluation and management of neurological emergencies are shared by neurologists, emergency medicine physicians, internists, hospitalists, and family practitioners. The way we care for these patients is defined by the work of those for whom we have tremendous respect.

When I was a resident at the University of Virginia, I loved to spend rainy afternoons in the library reading the monographs and essays of famous neurologists, many of whom had described the syndrome that would bear their name. I have always been as fascinated by neurologists as by neurology. While interviewing for residency, I shared a pizza with Roger Bannister. Over a cup of coffee at the ANA, Stan Prusiner explained his discovery of the prion protein drawing it for me on a napkin. Through the educational courses at the American Academy of Neurology, and in my role of Editor-in-Chief of *Seminars in Neurology*, I have had the incredible opportunity of getting to know and becoming friends with the great neurologists of our time.

When Springer asked me to edit a textbook on neurological emergencies, I thought about those afternoons in the library at the University of Virginia and how much it would mean to our colleagues and the next generation of neurologists to have a book that was written by neurologists that are Living Legends. Although this book is intended for neurologists, emergency medicine physicians, internists, family practitioners, and hospitalists, it is more than an ordinary textbook. It is a collection of the scholarly work of those who have spent their careers doing the work they love, advancing knowledge for the care of patients in their area of expertise. I am grateful that they would write for this textbook, greatly admire their work, and cherish their friendship.

This book is dedicated to the authors, and with love to my dear husband, Robert M. Pascuzzi, MD., and to our beautiful daughters, Annie and Jan.

Indianapolis, IN, USA — Karen L. Roos, MD

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Headache in the Emergency Department

1

Carrie E. Robertson, David F. Black, and Jerry W. Swanson

Abstract

Headache is the fourth most common reason for adult patients to present to the emergency department. Approximately two-thirds of these visits are for primary headache disorders, such as migraine, cluster, and tension-type headache. When evaluating a patient with headache in the emergency department, the physician must first decide if the headache represents a primary headache disorder or whether there is some other underlying etiology. Once a serious cause for headache has been excluded, the physician can focus on pain management. The first half of this chapter discusses the differential and diagnostic work-up of headaches with potentially dangerous etiologies. The last half addresses management strategies for primary headache disorders, with special focus on prolonged and intractable migraine headaches.

Keywords

Emergency department • Emergency room • Headache • Migraine • Migraine management • Pregnancy headache • Primary headache • Reversible cerebral vasoconstriction • Secondary headache • Status migrainosus • Subarachnoid hemorrhage • Thunderclap headache

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Introduction

Headache is an extremely common malady that causes numerous sufferers to present to the emergency department for relief and diagnosis. While some headaches are symptomatic of a serious underlying disorder, fortunately, most are of benign origin. Headaches can be classified within two major categories as outlined by the International Headache Society Headache

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Classification of Headache Disorders (ICHD-II) [1]: (1) primary headache disorders, and (2) secondary headache disorders. Primary headache disorders include such diagnoses as migraine, cluster headache, and tension-type headache. These are thought to represent an abnormal activation of the intrinsic pain system that may include both central and/or peripheral mechanisms. The predisposition to such disorders depends on both genetic and environmental factors.

A primary headache is diagnosed based on the patient's history and the absence of an identifiable underlying etiology. Imaging and laboratory investigations are most often used to help exclude secondary causes for headache. There is an extensive and varied list of possible sources of secondary headache, some of which include intracranial neoplasms, infections, hemorrhage, homeostatic derangements such as hypothyroidism, toxic exposure such as carbon monoxide poisoning, and many others.

This chapter will address the differential diagnosis of headache disorders likely to be seen in the emergency department as well as various diagnostic approaches utilized in the evaluation of secondary causes of headache. It will also outline several treatments for primary headache disorders. Therapeutic options for many secondary headache disorders are covered in other chapters of this book and are beyond the scope of this chapter. For an exhaustive list of all headache disorders and their diagnoses, the reader should see the ICHD-II [1] classification.

Epidemiology

The symptom of headache is a frequent reason for visits to the emergency department (ED). In the National Hospital Ambulatory Medical Care Survey in 2006, headache was the fourth most common reason that adults (patients 15 years and older) sought care in an emergency department. It was the third most common reason among women and the seventh most common reason among men. Overall, headache accounted for over 3.3 million emergency department visits which represented 2.8% of a total of over 119 million visits [2].

In the largest study of its kind, Goldstein and colleagues evaluated a representative sample of all of the adult ED visits for headache between 1992 and 2001, and found that approximately two-thirds of the visits were for a primary headache disorder [3]. Of those that presented with a secondary headache disorder, the vast majority were benign. In fact, only 2% of visits were found to be due to a serious pathologic etiology [3]. Previous studies also found that the majority of patients presenting to the emergency department with headache had primary headaches, with rates of secondary causes as low as 4% [3]. Certain clinical characteristics such as sudden onset, older age, and marked severity increase the probability of finding an underlying cause [3, 4].

Pathophysiology

A detailed discussion of the pathophysiology of all primary headache disorders is beyond the scope of this chapter; nevertheless, a brief overview of the pathophysiology of migraine is appropriate. Migraine headache likely is a result of alterations in central pain nociception regulation with consequential activation of meningeal and blood vessel nociceptors. Headache and its related neurovascular changes occur as a result of activation of the trigeminal system. Reflex links to the cranial parasympathetics comprise the trigeminoautonomic reflex. Activation leads to vasoactive intestinal polypeptide release and vasodilation [5].

Substance P, calcitonin gene-related peptide (CGRP), and neurokinin A are contained in trigeminal sensory neurons [6]. Excitation leads to release of substance P and CGRP from sensory C-fiber terminals [7], which contribute to neurogenic inflammation [8]. These substances interplay with blood vessels, causing dilation, plasma protein extravasation, and platelet activation [9]. Neurogenic inflammation is thought to sensitize nerve fibers (peripheral sensitization) resulting in

responses to formerly innoxious stimuli, like blood vessel pulsations [10], leading to, in part, the pain of migraine [11]. Central sensitization can also take place. After meningeal receptors are activated, neuronal activation takes place in the trigeminal nucleus caudalis [12] and in the dorsal horn in the upper cervical spinal cord [13, 14]. Positron emission tomography has demonstrated brainstem activation during migraine headache in areas approximating nociceptive pathways as well as in systems that modulate pain [15].

Clinical Features

Primary headaches are defined by their onset, duration, and associated features such as nausea/vomiting, visual aura, conjunctival tearing, rhinorrhea, etc. These discriminating features are broken down in detail under the differential diagnosis section. Some secondary headaches have classic presentations as well. The following is a list of clinical features on the history and exam that may be seen with particular headache etiologies.

History of Trauma

A history of trauma increases the chance of intracranial hemorrhage (subarachnoid, subdural, epidural, intraparenchymal), and may also precede a carotid or vertebral dissection. Cerebral venous thromboses are another uncommon but serious complication of closed head injury [16]. Trauma to the cribriform plate or dural sleeve could result in a cerebrospinal fluid (CSF) leak causing a low-pressure headache. Trauma resulting in fractures to the skull base or cervical vertebra can contribute to severe posterior head and neck pain. Minor head injuries can trigger a migraine in patients with a migraine history. Postconcussive headaches following closed head injury may mimic migraine or tension headaches and may have associated symptoms such as cervical pain, dizziness, cognitive impairment, and psychologic/somatic complaints such as irritability, anxiety, depression, fatigue, and sleep disturbance [17].

Fever or Known Infection

The presence of an infection elsewhere in the body should raise suspicion that the infection could have spread to the central nervous system. Patients should be assessed for the presence of neck stiffness/meningismus (resistance to passive movement of the neck), fever, or altered mentation. Recent medications for headache should be noted, as nonsteroidal anti-inflammatory drugs and acetaminophen may mask fever. Fever may also occur in the setting of vasculitis, malignancy, thrombosis, and subarachnoid hemorrhage. In subarachnoid hemorrhage, however, the fever tends to be delayed and is therefore less likely to be present on assessment in the ED.

Immunocompromise (HIV or Immunosuppression)

Patients with compromised immune defenses are at increased risk for possible CNS infections, including meningitis, encephalitis, or abscess. In addition, patients with AIDS are at increased risk of opportunistic CNS neoplasms, such as lymphoma. Certain immunosuppressants, such as cyclosporine, tacrolimus, and gemcitabine, are associated with an increased risk of posterior-reversible leukoencephalopathy. Other immunosuppressive agents, such as liposomal cytarabine, IVIG, intrathecal methotrexate, and azathioprine, can present with headache in the context of aseptic meningitis.

Concurrent Headache in Close Friends, Family, or Coworkers

If people with whom the patient has had contact have also developed new headaches, this should raise suspicion for an infectious or toxic exposure.

Infectious meningitis may present with isolated headache, or may have associated neck stiffness, meningismus, photophobia, nausea/vomiting, fever, or rash. If the symptomatic group of people have been in an enclosed environment (especially in winter), consider carbon monoxide poisoning. Carbon monoxide poisoning may have associated confusion, nausea/vomiting, chest pain, weakness, or dizziness. Tachypnea and tachycardia are the most frequent physical findings [18]. At carboxyhemoglobin levels greater than 31%, a cherry-pink coloring of skin is almost always seen [19]. However, a patient presenting mainly with headache would be expected to have milder levels, and would only rarely present with this classic coloring [20].

History of Cancer

A history of malignancy should raise concern regarding possible metastases to brain parenchyma or meninges. The most common metastases to the adult brain include lung (36–46%), breast (15–25%), and skin (melanoma) (5–20%). Almost any systemic tumor can metastasize to the brain, however, including kidney, colon, testes, and ovaries [21]. Headache in the setting of metastases may be nonspecific, but may be associated with nausea/vomiting, focal neurologic deficits, or seizures. They may be described as getting progressively worse in frequency or intensity, and may worsen in the supine position, with straining, or with cough. A malignancy-associated hypercoagulable state may place the patient at an increased risk of cerebral infarction and cerebral venous thrombosis (CVT). Headache may also occur as a side effect of chemotherapy (such as fluorouracil, procarbazine, or temozolomide). Associated anemia, hypercalcemia, or dehydration may also precipitate headaches.

Pregnancy

Primary headaches, such as tension-type headaches and migraine, often improve or remain unchanged during pregnancy [22–24]. Therefore, if a pregnant patient presents to the emergency department with her first-ever headache or a change in her headaches, the physician should be aggressive in his search for secondary causes.

For pregnant women after 20 weeks gestation, it is necessary to exclude preeclampsia/eclampsia. The presentation may be similar to migraine, and may even be accompanied by a visual aura. Associated altered mental status and seizures are concerning for eclampsia. CVT and reversible cerebral vasoconstriction may occur both during pregnancy and in the first few weeks after delivery [25]. Both carotid and vertebral dissections have been reported during pregnancy and following prolonged delivery [26–29]. Furthermore, the risk for ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage appears to be most elevated during the 2 days prior to, and the 1 day following, delivery. This risk remains somewhat elevated for 6 weeks postpartum [30, 31].

Visual Loss

There is a large differential for headaches presenting with associated visual loss. Bilateral visual loss may occur in the setting of papilledema with increased intracranial pressure from a mass or CVT. A pituitary mass can compress the optic chiasm and cause varying degrees of bilateral visual loss, especially in peripheral vision. Posterior reversible leukoencephalopathy syndrome (PRES) may present with both headache and bilateral visual loss, possibly associated with hypertension, and sometimes seizures. An ischemic stroke or mass in one hemisphere may present with headache and associated visual loss in one visual field (homonomous hemianopsia).

Monocular visual loss (amaurosis) with headache in a patient over age 50 is immediately concerning for temporal arteritis. Associated features may include temple tenderness, reduced temporal artery pulse, jaw claudication, increased erythrocyte sedimentation rate, fever, weight loss, or shoulder aching (polymyalgia rheumatica). Idiopathic intracranial hypertension

is often accompanied by transient visual obscurations which are episodes of visual loss lasting seconds; these are often monocular. Acute angle-closure glaucoma can present with rapidly progressive visual loss and associated eye pain or headache.

Headache Induced by Valsalva Maneuver

Exertion, cough, strain (Valsalva), bending over, or lifting heavy objects all tend to increase intracranial pressure. If a headache is precipitated by these maneuvers, consider structural processes affecting the posterior fossa, such as a Chiari malformation [32]. Patients with increased intracranial pressure may also have papilledema, nausea/vomiting, and worsening of their headache in a supine position. Disorders associated with intracranial hypertension such as CNS infection, masses, and hematomas may also worsen with these maneuvers. CVT can be associated with increased intracranial pressure due to venous hypertension. Idiopathic intracranial hypertension (pseudotumor cerebri) may present similarly, although this is a diagnosis of exclusion. It is important to note that there are benign headaches, such as cough headache, that may be triggered by cough or strain. Furthermore, migraineurs most often describe their headaches as worsening with activity in general, frequently including Valsalva maneuvers.

Pupillary Abnormalities

Patients presenting with a headache in the ED should routinely be examined for a Horner's syndrome (small pupil that does not dilate well in the dark with associated mild eyelid ptosis). Though a Horner's syndrome may occur in primary headaches such as trigeminal autonomic cephalalgias (TACs) and rarely migraine headaches, the presence of a Horner's syndrome should alert the clinician to the possibility of a carotid or vertebral dissection. A lung/neck malignancy can also cause a Horner's syndrome, and could be associated with headache in the setting of brain metastases. A larger pupil that reacts sluggishly to light may be seen with acute-angle glaucoma, or a lesion along the pupillary pathway (including optic neuropathy, cranial nerve III palsy, or a brainstem lesion).

Red Flags

A helpful mnemonic to remember the clinical "red flags" during evaluation of headache was developed by Dr. David Dodick [33]. He suggested using SNOOP, which stands for:

Systemic signs/symptoms/disease (fever, myalgias, weight loss, history of malignancy, or AIDS)
Neurologic signs or symptoms (altered mentation, seizure, papilledema, focal neurologic findings)
Onset sudden (thunderclap headache)
Older age (new onset of headache after age 50)
Pattern change from previous headaches (especially if rapidly progressive in severity or frequency)

When any of these are present, further labs, imaging, and/or spinal fluid analysis should be considered to investigate for a secondary cause of headache.

Approach to Diagnosis

The clinical history is the most valuable tool the clinician has to efficiently and accurately diagnose and treat a patient suffering from headache in the emergency department. The suddenness of onset and whether the patient has had similar headaches in the past can help guide differential diagnoses and management. A severe and unexpected headache that reaches peak intensity within seconds, often referred to as a "thunderclap headache," should be considered a neurologic emergency, and requires a systematic work-up (Fig. 1.1). It is tempting to assume that patients with a chronic history of headaches are

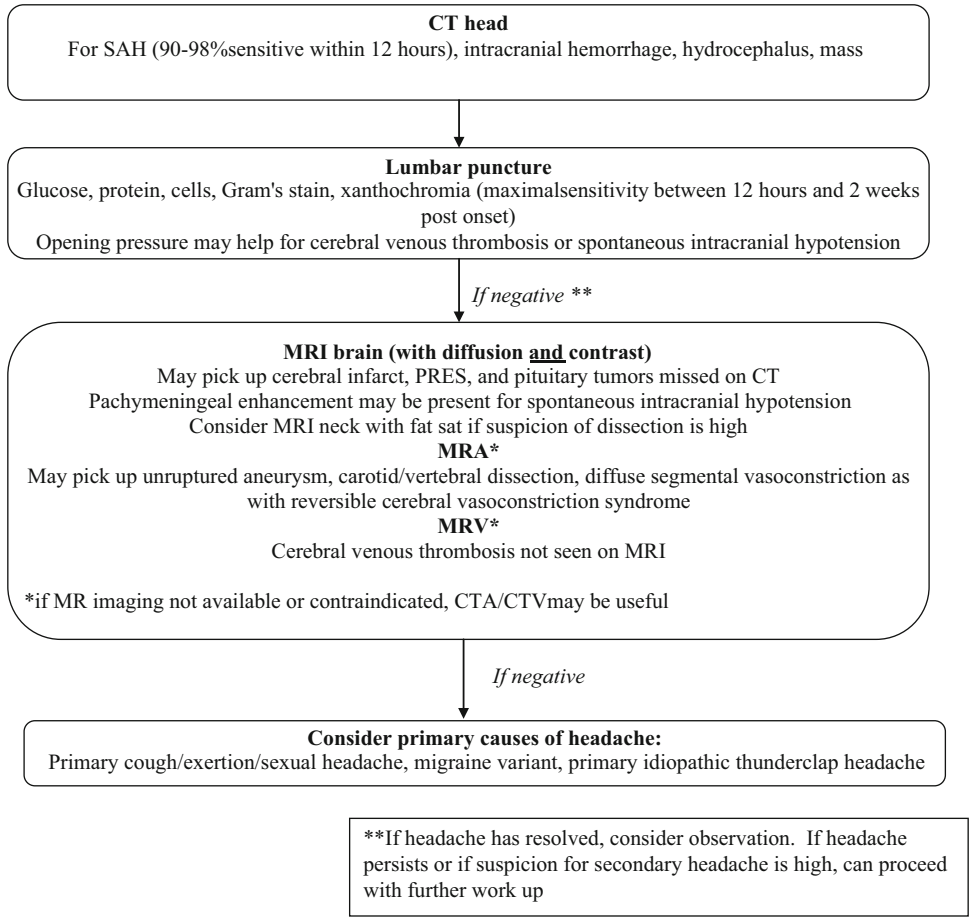

Fig. 1.1 Proposed work-up for sudden-onset headache

presenting to the emergency department for treatment only. However, if the headache has changed dramatically in pattern, a more thorough diagnostic evaluation should be performed. Answers to the following questions should be sought:

- Previous headache history/pattern? How does this headache compare with previous experiences?
- Onset and progression of this headache?
- Location and quality of pain?
- Radiation?
- Severity?
- Duration?
- Any fluctuation in intensity? If so, what makes it better or worse? Specifically, is the severity affected by certain positions, times of day, cough, Valsalva, or sleep?
- Any associated symptoms such as:
  - Nausea/vomiting
  - Photophobia/phonophobia
  - Visual changes (blurring, diplopia, flashing/colorful lights)
  - Whooshing/roaring tinnitus
  - Weakness, numbness, or difficulty walking
  - Autonomic features (tearing, conjunctival injection, rhinorrhea, flushing/sweating)
  - Seizures
- Current pregnancy, infection/fever, immunocompromised state?
- Current medications (anticoagulants, nitrates) and any recent medication changes?
- Past medical history of recent trauma, cancer, previous blood clots/miscarriages, or

polycystic kidney or connective tissue disease (last two may increase chance of aneurysm and therefore subarachnoid hemorrhage)?
- Family history of migraines, clots, bleeding?
- Any family members, friends, or coworkers also suffering from new headache?

A general examination with special attention to vital signs is necessary, followed by a careful examination for any focal neurologic findings. This should include:
- Detailed eye exam (for papilledema, pupillary abnormalities, and visual field abnormalities)
- Auscultation for carotid, temple, or orbital bruits
- Palpation of bilateral temple regions to assess for prominent superficial temporal arteries with reduced pulsation
- Identification of any reported areas that increase or cause pain such as the "trigger zones" in trigeminal neuralgia
- Examination of cranial nerves, strength, and sensation, with special attention to symmetry
- Deep tendon reflexes and plantar reflexes (Babinski sign)
- Unless impossible, the gait should be observed for subtle ataxia/weakness. This may also help elicit positional changes in headache severity

Labs and Imaging

Given the wide variability of secondary headache presentations, it is often difficult to identify which patients require more evaluation than just a history and physical examination. As mentioned previously, if there are any associated red flags such as immunocompromised state, older age, or a change in the pattern of headache, further work-up should be considered. A sudden onset, extremely severe, "worst headache of my life" presentation should be treated as a medical emergency and be evaluated in a systematic fashion for subarachnoid hemorrhage or alternative etiologies (see Fig. 1.1).

Serologic Testing

Initial blood tests for headache might include a CBC to look for leukocytosis or glucose/electrolytes to look for metabolic derangements and any evidence of dehydration (especially if vomiting). Sedimentation rate should be considered in any patient older than age 50 with a new type of headache, to screen for giant-cell (temporal) arteritis. Coagulation factors (PT and PTT) should be considered if there is concern for hemorrhage, such as with a thunderclap presentation or if the patient is on anticoagulants. If the headache has associated altered mentation, consider liver function tests and a drug/toxicology screen. If carbon monoxide poisoning is suspected, testing for carboxyhemoglobin may also be useful.

ECG

Although rare, cardiac ischemia may present with isolated headache, and is referred to as "cardiac cephalalgia." If a patient has cardiac risk factors, associated shortness of breath, or a new headache that is precipitated by exertion, consider an ECG and/or stress testing to look for ischemia [34].

Computed Tomography of the Head

Computed tomography (CT) is the most widely available brain imaging technique in the emergency department, and in most cases is adequate to rule out mass effect (from a tumor, abscess, stroke, or other lesion) and acute blood (subarachnoid, epidural, subdural, or intraparenchymal). It is important, however, to understand that CT has its limitations. CT of the head will miss subtle, early, or small infarcts, and may also miss small subarachnoid and subdural hemorrhages. With a well-read head CT, the sensitivity for subarachnoid hemorrhage in the first 12 h is around 90–98% [35–37]. CT becomes less sensitive with increasing time from the onset of headache, with a sensitivity of about 58% at 5 days and about 50% at 1 week [35]. Sensitivity for any type of hemorrhage is reduced if the hematocrit is less than 30% [38]. Lesions and mass effect in the posterior fossa can also be difficult to visualize, especially with a poor-quality CT, given the artifact from surrounding bone structures.

A CT head is normally performed without contrast in the emergency room. However, it may be reasonable to add contrast if there is suspicion for CVT or metastases.

Lumbar Puncture

When infection is suspected, it is necessary to analyze spinal fluid for inflammatory cells, protein and glucose concentrations, Gram's stain, and cultures. Ideally the patient should have this procedure in the lateral decubitus position, and opening pressure should be measured. Normal opening pressure is 5–22 cm H_2O. Care must be taken to relax the patient with legs extended when measuring the opening pressure, to avoid a spurious elevation of the measurement.

The opening pressure may be elevated with many pathologic processes, including infection or inflammation of the meninges. It may also be elevated with mass effect, increased venous pressure (such as from CVT), idiopathic intracranial hypertension, or metabolic disorders causing cerebral edema (anoxia, hypertensive encephalopathy, hepatic encephalopathy). If there is a concern for a mass lesion, a head CT should be performed prior to lumbar puncture. If a mass lesion is present, the lumbar puncture should be deferred due to the risk of herniation. It may be reasonable to skip the head CT if the following are not present: age greater than 50, immunocompromised state, previous brain injury (stroke, infection, mass), seizures, altered mentation, or focal neurologic findings [39].

If subarachnoid hemorrhage is a consideration and the head CT is negative for blood, a lumbar puncture is required to look for xanthochromia, a yellowish appearance to the CSF. In subarachnoid hemorrhage, xanthochromia is caused by blood breakdown products, such as oxyhemoglobin and bilirubin. Xanthochromia may also be positive if the CSF protein concentration is more than 150 mg/dL, if there are more than 400 red blood cells (RBCs), or with hyperbilirubinemia. Xanthochromia may be undetectable if tested too early (less than 12 h after a hemorrhage) or too late (longer than 2 weeks) [38]. If available, spectrophotometry is significantly more sensitive than visual inspection for xanthochromia [40, 41], though specificity seems to be lower [42].

In the event of a "traumatic spinal tap," RBCs may be elevated in the CSF. To try and differentiate whether the RBCs are from the lumbar puncture or an acute hemorrhage, it is reasonable to compare the number of RBCs in the first tube to the last tube of CSF. Usually, if the red blood cells are from the procedure, the blood will become progressively dilute and there will be fewer RBCs in the last tube drawn. Keep in mind, however, that if the number of RBCs in the last tube is not zero, it does not necessarily rule out subarachnoid hemorrhage [38].

MRI

MRI is not frequently available in the emergency department for evaluation of headache. Furthermore, there are limited instances where an MRI would be necessary in an emergent situation. One of the cases where a clinician might consider MRI is in a patient with persistent thunderclap headache with a negative head CT and lumbar puncture. If there are no other historical clues to diagnosis, an MRI provides the best visualization of the posterior fossa, and may demonstrate cerebral infarcts or posterior leukoencephalopathy (PRES) missed on CT. Pituitary tumors and colloid cysts that were not evident on CT may also be more conspicuous on MRI. Subdural fluid collections and pachymeningeal enhancement may be noted in spontaneous intracranial hypotension. If an MRI is to be performed in a patient with normal kidney function, it should be with diffusion and contrast imaging to increase sensitivity. If the patient has reduced kidney function, especially in the setting of hemodialysis or prior renal transplant, the benefits of using contrast (gadolinium) should be weighed against the risk of causing the rare, but sometimes fatal, condition of nephrogenic systemic fibrosis (NSF).

Vascular Imaging

If there is suspicion for dissection, the patient should be evaluated with carotid ultrasound, MRA, or CTA (of both the head and neck). If the emergency department is equipped to perform an MRI, MRI with fat saturation sequences will often identify the mural hematoma. An MRA or CTA will help delineate the extent of a dissection. MRA may also help identify unruptured aneurysms or diffuse vasoconstriction. If the patient has a contraindication to MR imaging, such as a pacemaker, then a CTA would be

preferred. An MRV or CTV may be helpful in identifying cerebral venous thromboses that were not identified on CT or MRI.

Differential Diagnosis

Primary Headaches

As previously described, the majority of patients presenting to the emergency department with headache have a primary headache [3]. Thus, clinicians must have a basic understanding of the various types of primary headaches, their presentations, and their management. The following list is not comprehensive, but covers some of the more common primary headaches. Also listed are some rare, but uniquely presenting headaches that may mimic more serious conditions.

Migraine

According to the diagnostic criteria of the International Headache Society (ICHD-2), a diagnosis of migraine without aura requires at least five attacks lasting 4–72 h with nausea/vomiting or photophobia/phonophobia. At least two of the following must also be present: unilateral location, pulsating quality, moderate to severe pain intensity, or worsening of pain with physical activity. Migraine with aura is similar, but is associated with focal neurologic symptoms that typically last for 5–60 min. Aura (when present) typically precedes the headache, but may occur during the headache as well. Visual auras are most common, and tend to occur unilaterally (hemianopia) with a combination of scotomas (blurred or graying visual areas) and positive phenomenon such as sparkling/flashing lights or colors. Sensory auras also tend to be a combination of negative features (numbness) and positive features (tingling), and may occur in a cheiro-oral (hand and face) distribution [43]. These tend to slowly march over 5–30 min. Unilateral weakness may accompany hemiplegic migraines, while brainstem symptoms, such as dysarthria, vertigo, and diplopia (with or without visual field defect) may be seen in basilar-type migraines. A reduced level of consciousness or transient loss of consciousness may also accompany basilar artery-type migraines.

In the emergency department, neurologic deficits should not be assumed to be related to migraine headache unless the patient has a clear history of the same symptoms with their typical migraine aura. Often the difficulty with migraineurs in the emergency department is not that of diagnosis, but of treatment. This is especially true in patients with status migrainosus, a debilitating attack of an otherwise typical migraine that lasts longer than 72 h. See the treatment section for recommendations on managing migraine in the emergency department.

Tension-Type Headache

A tension-type headache is typically described as a bilateral, nonthrobbing pressure or tightness that is mild to moderate in intensity and does not worsen with physical activity. It may last minutes to days and can have associated muscle spasm, especially in the cervical region. There may be photophobia or phonophobia, but usually no nausea or associated aura.

Cluster Headache and Other Trigeminal Autonomic Cephalalgias

The TACs are a group of headaches associated with autonomic symptoms, including conjunctival injection, tearing, nasal congestion, rhinorrhea, sweating, ptosis, eyelid edema, and miosis. They are divided into subcategories according to their duration.

Cluster Headache

- The longest attack occurs in the most well known of these disorders, cluster headache. These patients present with severe attacks of unilateral pain in the orbital, supraorbital, or temporal areas, with typical autonomic features ipsilateral to the pain. Cluster headaches usually build in intensity, lasting 15 min to 3 h, and may recur up to eight times a day. During an attack, the pain is extremely severe and the patient may seem restless, and may pace back and forth, not wanting to lie down. These may occur at similar times of day, and may recur for weeks or months (clusters), separated by remission periods. Cluster headaches are three

times more prevalent in men and may be inherited in about 5% of cases [1].

Paroxysmal Hemicrania

- Episodic paroxysmal hemicrania is similar to cluster headache in that the patient has periods of repeated attacks separated by periods of remission. The attacks tend to be of shorter duration than cluster, lasting 2–30 min, and are described as severe unilateral orbital, supraorbital, or temporal pain accompanied by the autonomic symptoms described earlier. These typically occur more than five times a day from 7 days to 1 year, with pain-free periods of 1 month or longer [1]. In some patients, the attacks may be precipitated mechanically by bending or neck movement. If a patient has attacks for more than 1 year without remission, the headaches are referred to as chronic paroxysmal hemicrania [1]. By definition, attacks are prevented completely by therapeutic doses of indomethacin.

Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing/cranial autonomic features (SUNCT)

- Similar to the other TACs, SUNCT headaches are described as unilateral stabbing or pulsating pain in the orbital, supraorbital, or temporal region associated with ipsilateral autonomic symptoms. As evidenced by their names, these headaches are the shortest in the group. They may last 5 sec to 4 min, and occur 3–200 times per day [1]. Similar to trigeminal neuralgia, these paroxysmal pains may be triggered by chewing, smiling, light touch, or a cool breeze.

Benign Cough Headache

Benign cough headache is usually bilateral, short lasting (1 sec to 30 min), and only occurs in association with coughing or straining. It occurs more often in men over the age of 40 [1]. Symptomatic cough headache may be caused by Arnold Chiari malformation (Fig. 1.2), posterior fossa mass lesions, cerebral aneurysms, or other carotid/vertebral disease [1].

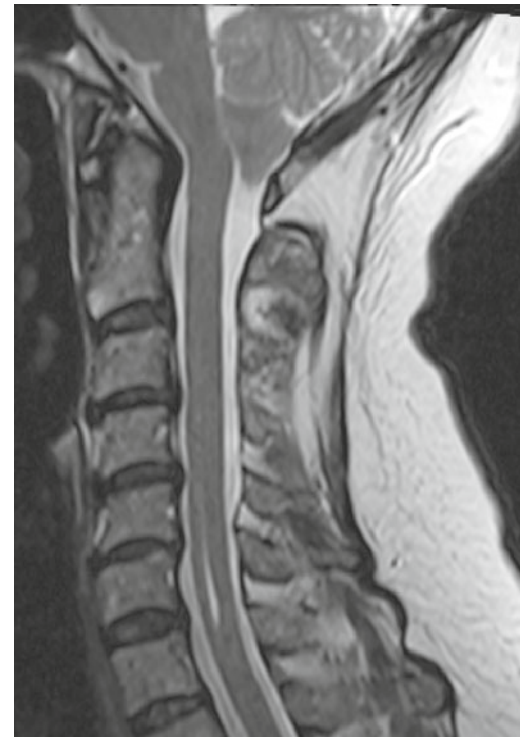

Fig. 1.2 Chiari I malformation. Sagittal unenhanced T2-weighted MRI demonstrates descent of the cerebellar tonsils >5 mm below the foramen magnum with an associated syrinx at C6. Note that without gadolinium and clinical screening, a patient with low CSF pressure from a CSF leak may be misdiagnosed as having a Chiari 1 malformation

Benign Sexual or Orgasmic Headache

Two types of headache may occur with sexual activity. One is a dull aching pain in the head and neck (similar to tension headache) that intensifies with increasing sexual excitement. The other is an explosive (or thunderclap) type of headache that occurs with orgasm. With an orgasmic headache, it is important to rule out subarachnoid hemorrhage, reversible cerebral vasoconstriction syndrome, and other sources of thunderclap headache [1].

Benign Exertional Headache

It is not uncommon for headaches, especially migraine, to worsen with exertion. However,

a throbbing headache lasting 5 min to 48 h, brought on by and occurring only with exertion, may represent benign exertional headache [1]. In the emergency department, such a patient should also be evaluated for exertional cardiac ischemia, as headache may sometimes be the only presenting symptom [34].

Secondary Headaches

While primary headaches present more often, the goal in the emergency department is not necessarily to diagnose which primary headache is present, but rather to rule out sources for secondary headache. Amongst the secondary headaches, the most concerning are those that present with an explosive, debilitating, or "thunderclap" presentation. When a patient presents in this way, the first goal is to rule out a subarachnoid hemorrhage. There are many other headaches in which the patient may describe "the worst headache of their life" with acute onset. These are outlined in Table 1.1. More detailed descriptions of some of these are included in the text below.

Subarachnoid Hemorrhage

While the classic thunderclap headache should not be missed, some patients with subarachnoid hemorrhage present with more subtle symptoms (Fig. 1.3). Any headache that is unusual for the patient, especially if there is associated neck pain

Table 1.1 Differential for thunderclap headache

Headache type	What to look for	Testing
Subarachnoid hemorrhage	Sudden onset May have decreased consciousness, possible neck stiffness	CT without contrast. If no acute blood, check CSF for xanthochromia
Intracranial hemorrhage	Focal neurologic signs, altered mentation, possible seizures	CT without contrast
Cerebral venous sinus thrombosis	Headache may be postural (worse supine) and may worsen with Valsalva. Check for papilledema	MRV preferred. CT *with contrast* may reveal Delta sign. CSF may be normal or have increased pressure or elevated protein concentration
Cervicocephalic arterial dissection (carotid or vertebral)	May have associated neck pain Check for presence of Horner's sign and other neurologic deficits	MRI and MRA of head and neck. Can start with carotid ultrasound or get CTA if MRI not available
Pituitary apoplexy	Often have nausea May have change in consciousness, visual loss, or double vision May present with pituitary insufficiency	Start with CT if acute to look for blood. However, MRI may be required
Acute hypertensive crisis	Presence of hypertension, usually more than 180/110	Need to rule out other causes of headache with high BP ECG Consider CT head for blood, stroke, or PRES MRI is more sensitive for PRES
Spontaneous intracranial hypotension	Postural headache, better supine, worse upright	MRI to look for pachymeningeal enhancement and low-lying cerebellar tonsils Can check LP for opening pressure
Reversible cerebral vasoconstriction syndrome (RCVS)	May present with recurrent thunderclap headache, occipital or diffuse May have photophobia, nausea	Cerebral angiogram is gold standard; can check MRA or CTA
Ischemic stroke	New neurologic deficits, especially in a vascular distribution	MRI with diffusion-weighted imaging; if large or subacute/chronic, may show on CT

(continued)

Table 1.1 (continued)

Headache type	What to look for	Testing
Third ventricular colloid cyst	Headache often positional, can be followed by syncope or even death if hydrocephalus is severe	CT often sufficient, but MRI may be required
Acute expansion of mass in posterior fossa	May have reduced consciousness, cerebellar signs, or asymmetric pupils if associated with herniation	CT head should show mass effect
Intracranial infection (e.g., bacterial meningitis)	Fever, chills, meningismus, leukocytosis	CSF studies; MRI may show meningeal enhancement
Primary sexual or exertional headache	Sudden onset before, during, or right after orgasm or peak of exertion. Look for previous episodes	Diagnosis of exclusion (especially if this is the first occurrence); specifically need to rule out aneurysm with SAH and RCVS
Primary cough headache	Sudden onset with cough or strain, lasting minutes (1 s to 30 min)	Diagnosis of exclusion
Glaucoma	Slowly responsive dilated pupil, with ipsilateral pain	Ophthalmology consult
Primary thunderclap headache	Maximum intensity in <1 min. Lasts 1 h to 10 days	Diagnosis of exclusion

Modified list from Schwedt et al. 2006 [44]

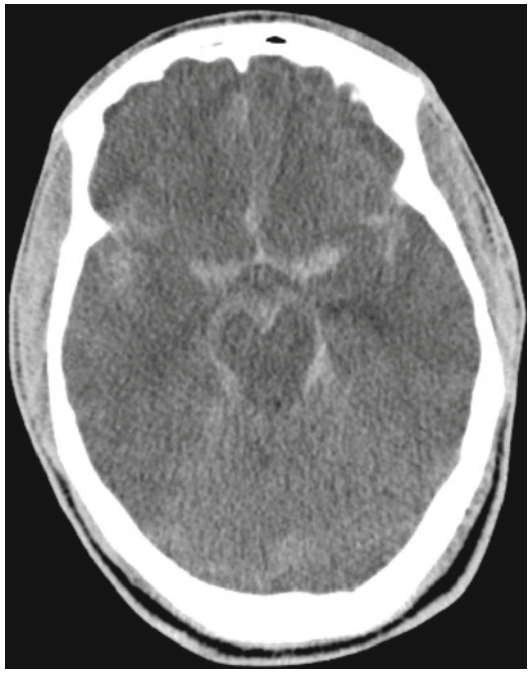

Fig. 1.3 Acute subarachnoid hemorrhage. Axial, unenhanced head CT demonstrates acute, high-attenuation subarachnoid blood products surrounding the brainstem, and filling the suprasellar cistern, sylvian fissures, and interhemispheric fissure

or stiffness, should raise the possibility of a subarachnoid hemorrhage. Evaluation should include a head CT followed by a lumbar puncture if negative (see approach to diagnosis).

Other Intracranial Hemorrhage

Hemorrhage into brain parenchyma may present similarly to a subarachnoid hemorrhage. If the blood tracks into the CSF, it may cause meningeal irritation and neck stiffness. Focal neurologic symptoms, including seizures and altered mentation, may be present depending on the size and location of the hematoma. Epidural and subdural hematomas may present with headache, often following trauma. A careful history must be taken as the associated trauma may be remote with subdural hematomas. Be concerned about hemorrhage in a patient on anticoagulation therapy with a new-onset headache, especially if they are older.

Cerebral Venous Thrombosis

Presentation depends on the size and location of the thrombosis (Fig. 1.4). The most frequent symptom is headache, which may be subacute

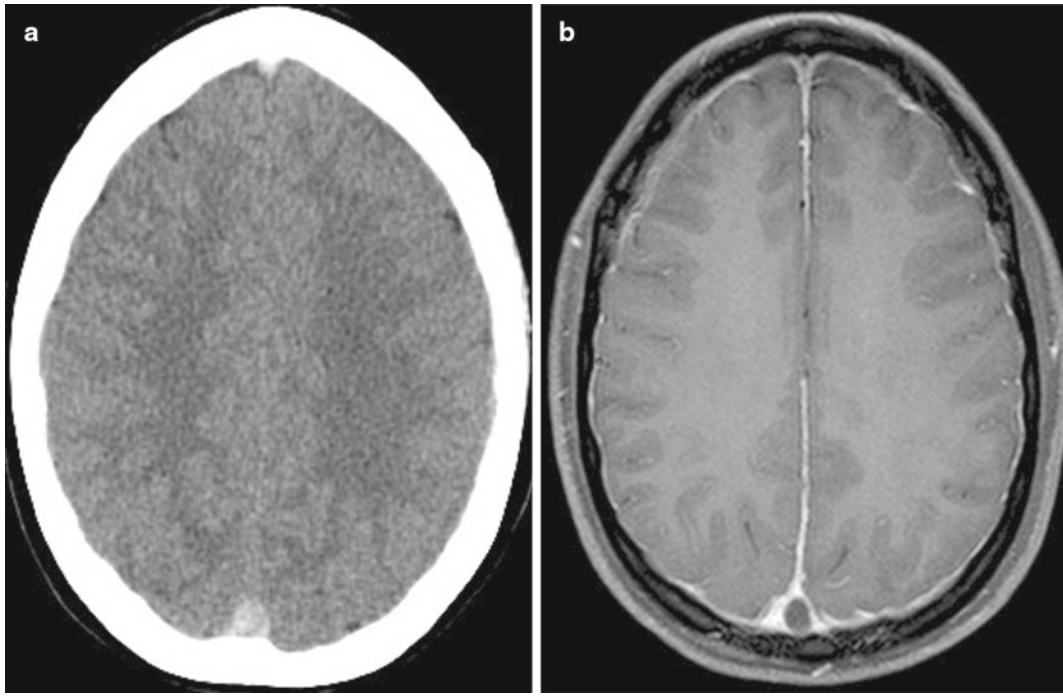

Fig. 1.4 Superior sagittal sinus thrombosis. Axial, unenhanced head CT (**a**) demonstrates high-attenuation material consistent with thrombus within posterior aspect of the superior sagittal sinus. T1-weighted, gadolinium-enhanced MRI (**b**) demonstrates a filling defect ("empty delta sign") within the superior sagittal sinus due to thrombus

over days or a more sudden "thunderclap" presentation. A large deep venous thrombosis may cause increased intracranial pressure, leading to blurred vision, nausea/vomiting, positional headache, and occasionally a cranial nerve VI palsy. This can progress into subacute mental status changes and coma. A small cortical venous thrombosis may present with focal neurologic findings or seizures [45]. Risk factors for CVT are similar to risk factors for other venous thrombosis, and include infection, malignancy, oral contraceptives, pregnancy/postpartum, and history of a hypercoagulable state.

On a head CT with contrast, the classic appearance of a CVT is the "empty delta sign," which is the empty-appearing triangle created when the confluens sinuum fails to fill with contrast. This sign is present 25–30% of the time, but more often the CT shows nonspecific focal or generalized edema, gyral enhancement, or enhancement of the falx/tentorium [45]. Diagnosis relies on imaging of the cerebral venous system, with either an MRV or CTV (if MR imaging is contraindicated or difficult to obtain). Anticoagulation appears to be safe in these cases, and may even improve outcome. Even with anticoagulation, the mortality is around 5–10% [46].

Meningitis

The presence of fever, neck stiffness, meningismus, or altered mentation associated with headache is concerning for inflammation of the meninges, or meningitis. Unfortunately, the presentation may be subtle. In one study of bacterial meningitis, only 44% of patients presented with the classic triad of fever, neck stiffness, and change in mental status. However, 95% had at least two of the following four signs and symptoms: headache, fever, neck stiffness, and altered mentation [47]. Some patients present with headache in isolation.

In the emergency department, it is necessary to first rule out infectious etiologies of meningitis, including bacteria, viruses, fungi, and

mycobacteria. This should be done with a blood culture and a lumbar puncture for CSF (with or without preceding CT, see lumbar puncture section). Meningitis may be due to noninfectious etiologies as well, and present with headache, with or without fever. Etiologies for noninfectious meningitis include leptomeningeal metastases, systemic autoimmune diseases, or medications (NSAIDs, IVIG, intrathecal chemotherapy).

Cervicocephalic Dissection

Carotid and vertebral dissections are often associated with head or neck pain. In one study, 8% of 245 patients with cervical dissections presented with head and/or neck pain as their only symptom [48]. In all but one of these cases, the pain was different from their previous headaches. While it is difficult to recommend extensive testing for dissection in every new-onset headache, this should at least be on the differential. Investigations for dissection should be considered in an otherwise unexplained acute or thunderclap headache, or with a new progressive headache associated with neck pain, a Horner's syndrome, cranial nerve palsies, monocular vision loss (amaurosis fugax), or other focal neurologic signs. A history of preceding trauma to the neck, even minor trauma such as chiropractic neck manipulation or whiplash from a roller coaster ride, increases the suspicion for dissection.

Ischemic Stroke

Headache is not uncommon in the setting of ischemic stroke, especially with large strokes. If a patient has a history of migraine headaches, the ischemic stroke may trigger one of their typical headaches. This can make diagnosis quite challenging as migraineurs can have neurologic symptoms as part of a migraine aura (see migraine section). If a migraine patient is presenting in the emergency department with a typical migraine, but has a new or changed neurologic aura, consider the possibility of ischemia or other focal neurologic injury.

Reversible Cerebral Vasoconstriction Syndrome

Reversible cerebral vasoconstriction syndrome (RCVS) is characterized by a sudden severe thunderclap headache associated with vascular narrowing in the vessels of the circle of Willis and its branches. The term represents a group of disorders including Call-Fleming syndrome, benign angiopathy of the CNS, postpartum angiopathy, drug-induced vasospasm, migrainous vasospasm, and migrainous angiitis [25, 49]. Headaches tend to last minutes to hours, and may recur over a few days to weeks. Because of the vasoconstriction, most patients also have focal neurologic deficits, and one-third of patients have seizures. CSF is normal or near normal (protein <80 mg/dL, WBC <10 cells mm^3), [25] and there may be a slight elevation of ESR [49]. The gold standard for diagnosis is conventional angiography which shows multifocal segmental vasoconstriction, reversible within 12 weeks after onset. MRA or CTA is the recommended first-line imaging procedure, however. MRI and CT may be normal, may show features similar to posterior reversible encephalopathy syndrome (PRES), or may show evidence of intracranial hemorrhage, especially cortical subarachnoid hemorrhage. Patients typically do well even without treatment, although cerebral infarction may occur [50]. There are some case reports suggesting possible benefit with calcium channel blockers such as nimodipine, but there has not been a well-designed trial to explore this further [49].

Low-Pressure Headache

When there is a decrease in CSF, patients may develop an orthostatic headache that is worse in the upright position and better while recumbent (Fig. 1.5). Low-pressure headaches are often throbbing (not always) and either bilateral or holocephalic. These may occur as thunderclap headaches and occasionally present only with exertion. There may be a variety of associated symptoms, many of which are also orthostatic in nature. These include dizziness, hearing changes with a sense that sounds are muffled (from stretching of cranial nerve VIII or changes in perilymphatic pressure), visual blurring, reduced consciousness (from compression of the diencephalon), and ataxia or other gait disorders (from compression on the posterior fossa and spinal cord) [51].

The depletion of CSF may be from hypovolemia, overshunting of CSF, or a CSF

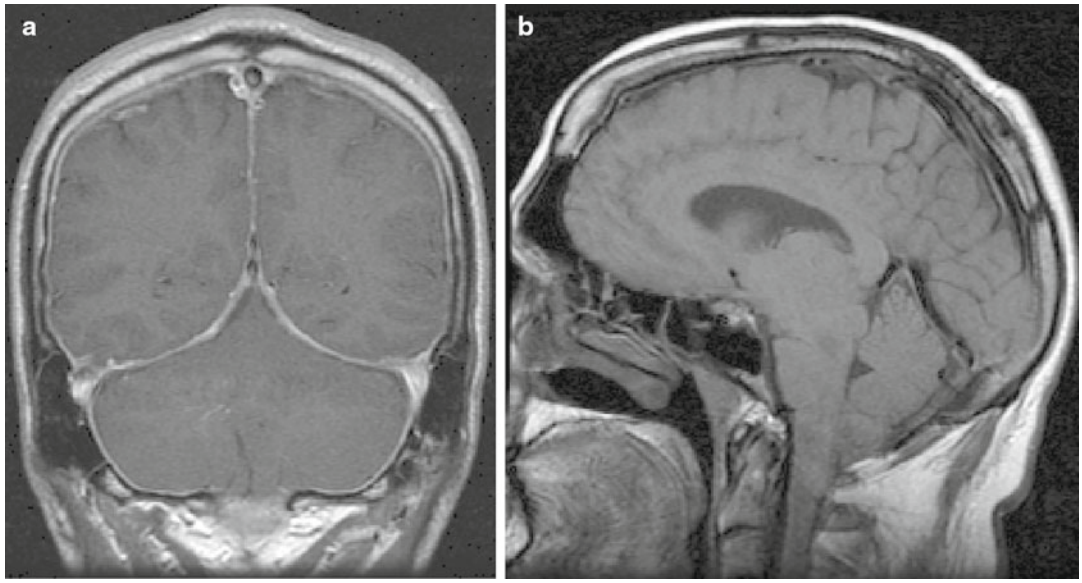

Fig. 1.5 Intracranial hypotension. Coronal T1-weighted, gadolinium-enhanced MRI (**a**) demonstrates prominent pachymeningeal enhancement. Sagittal T1-weighted, unenhanced MRI (**b**) shows descent of the cerebellar tonsils through the foramen magnum with flattening of the pons against the clivus consistent with "brain sag"

leak. A history of recent lumbar puncture, epidural, spinal surgery, or motor vehicle accident suggests a persistent traumatic CSF leak. Spontaneous CSF leaks may occur through weak meningeal diverticula or weak dura, and may be associated with connective tissue disorders [51]. A head CT is usually unremarkable, although subdural fluid collections are sometimes appreciated. On MRI, typical findings include pachymeningeal enhancement, descent of the cerebellar tonsils (resembling Chiari I malformation), crowding of the posterior fossa, decreased ventricle size, and subdural fluid collections (typically bilateral). Lumbar puncture is not necessary for diagnosis, but when it is performed, the opening pressure may be normal to low and CSF protein concentration may be normal to high. Pleocytosis (WBC in the 10–50 cells/mm^3 range, rarely up to 220 cells/mm^3) may also occur [52, 53]. Most of these are self-limited and respond well to bed rest, caffeine, and increased fluid intake. However, a persistent headache may require an epidural blood patch by anesthesiology. Severe or persistent cases may need to be further evaluated with CT myelography to identify the leak for possible surgical repair.

Hypertensive Crisis and PRES

In a study of 50 patients presenting with hypertensive urgency (blood pressure greater than 180/110), the two most common presenting complaints were headache (42%) and dizziness (30%) [54] (Fig. 1.6). With hypertensive crisis, there is also evidence of end-organ damage such as stroke, hypertensive encephalopathy, or acute pulmonary edema. A patient presenting with headache and marked elevation of blood pressure presents a diagnostic dilemma. Severe hypertension may be a source for headache, but severe headache pain may also result in secondary elevation of blood pressure. Furthermore, a patient may have an underlying process, such as a hemorrhagic or ischemic stroke, that is associated with both. The possibility of ischemic stroke is particularly worrisome because lowering blood pressure could potentially exacerbate cerebral ischemia. Before attempting to lower blood pressure, a careful neurologic examination should be performed to look for signs of ischemic stroke.

Posterior reversible leukoencephalopathy, also termed posterior reversible encephalopathy syndrome (PRES), is a syndrome involving vasogenic edema preferentially affecting the white matter of

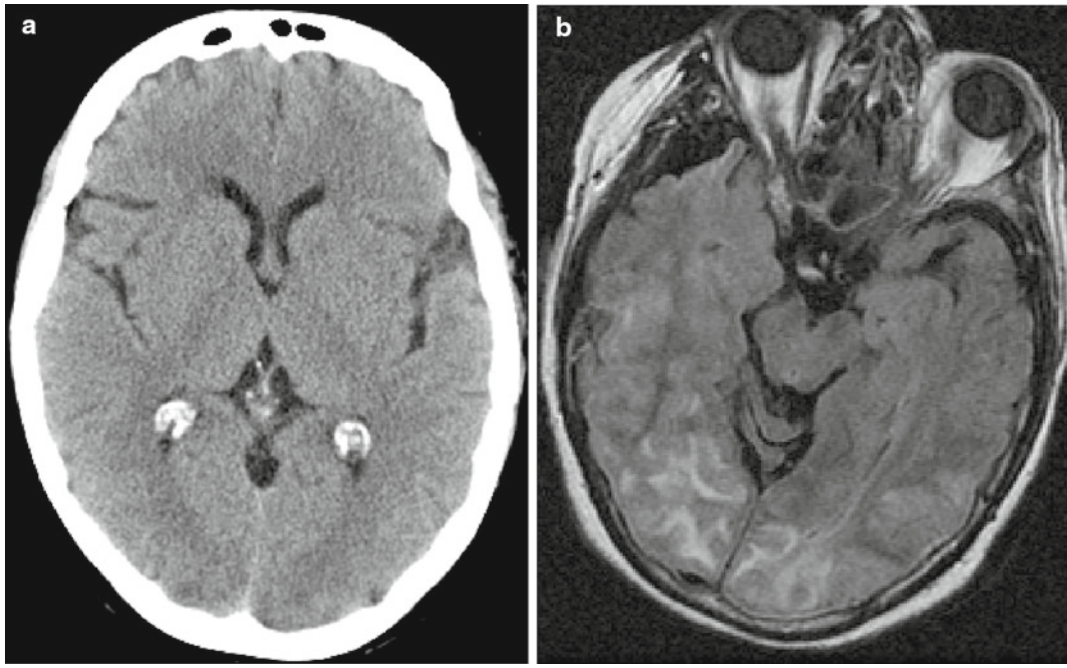

Fig. 1.6 Posterior reversible leukoencephalopathy syndrome (PRES). Axial unenhanced CT (**a**) shows subtle loss of differentiation between *gray and white matter* within the occipital lobes. Axial FLAIR MRI (**b**) demonstrates abnormal T2 signal in the posterior white matter

the posterior brain, including the occipital lobes and cerebellum. Symptoms may include headache, nausea/vomiting, seizures, altered mentation, and sometimes other focal neurologic signs, such as bilateral visual loss [55]. The name is somewhat misleading because PRES does not necessarily have to be posterior, reversible, or limited to white matter.

PRES may occur with hypertensive encephalopathy, as well as preeclampsia/eclampsia, and some immunosuppressive agents such as cyclosporin, tacrolimus, and IVIG. When diagnosing PRES, MRI is more sensitive than CT and demonstrates an increased T2 signal abnormality. Posterior reversible leukoencephalopathy may sometimes be noted as hypodense regions on a head CT.

Pituitary Apoplexy

Pituitary apoplexy occurs when a pituitary tumor (typically a benign adenoma) spontaneously hemorrhages or when it outgrows its blood supply (causing pituitary infarct) (Fig. 1.7). Patients may present with a sudden-onset severe headache, mimicking subarachnoid hemorrhage. They may have associated nausea, visual loss, or double vision. On occasion, they may present with a change in consciousness or adrenal failure. A head CT may show changes consistent with acute hemorrhage, but may miss subtle hemorrhage or infarct. If pituitary apoplexy is suspected and the CT is negative, consider MRI [56].

In addition to neurosurgery (for possible urgent transsphenoidal resection), an endocrinologist is often involved acutely and in recovery to help manage high-dose corticosteroids and other hormonal replacements [57].

Idiopathic Intracranial Hypertension

The typical patient is an obese female presenting with headache that is daily, severe, throbbing, lasts hours, and may wake the patient from sleep. Patients may have associated nausea/vomiting, transient visual obscurations or loss of vision (from papilledema), sparks/flashes in their vision, or horizontal diplopia. They may have

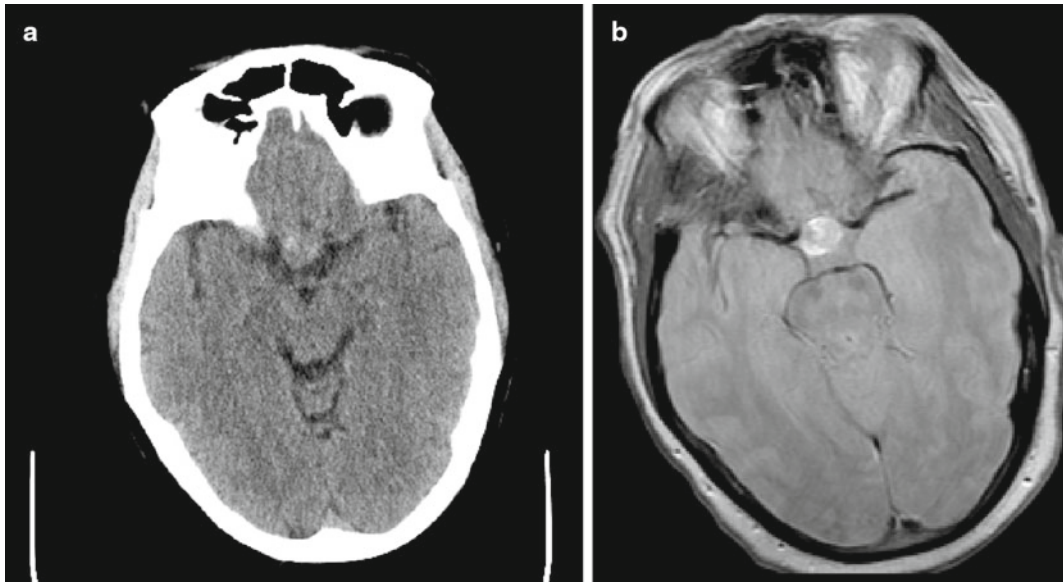

Fig. 1.7 Pituitary apoplexy. Unenhanced CT (**a**) and MRI (**b**) demonstrate acute hemorrhage into a pituitary adenoma

associated tinnitus that is synchronized with their pulse [58]. Most work-up for idiopathic intracranial hypertension is performed as an outpatient. However, if the patient presents to the emergency department for evaluation, a head CT would need to be performed to exclude a mass lesion. A lumbar puncture should show normal composition and an elevated CSF pressure (>20 cm H_2O in the nonobese, >25 cm H_2O in the obese). As this is a diagnosis of exclusion, at some point the patient should have further testing such as an MRI and MRV to exclude sources for venous hypertension (from a dural venous thrombosis, AVM, or AV fistula) [59, 60]. In one study, 9.4% of 106 patients with presumed idiopathic intracranial hypertension had a CVT [61].

Management generally begins with treatment of obesity and discontinuing any medications associated with intracranial hypertension, such as nitrofurantoin, retinoic acid, excessive vitamin A, anabolic steroids, tetracycline, etc. [58]. Medical therapy with acetazolamide or furosemide may be attempted. If the patient fails therapy or has progressive visual loss, a surgical procedure such as optic nerve sheath fenestration or shunting may be required [59, 60].

Postconcussive

Postconcussive headaches following closed head injury may mimic migraine or tension headaches. Furthermore, trauma may trigger a typical migraine in a migraineur. Sometimes postconcussive headaches are part of a syndrome of symptoms including cervical pain, dizziness, cognitive impairment, and psychologic/somatic complaints such as irritability, anxiety, depression, fatigue, or sleep disturbance [17]. Imaging performed on a patient with a headache following trauma is primarily done to rule out traumatic lesions such as intracranial hematomas. While subtle MRI changes may be seen later, there are no specific imaging findings to help diagnose a postconcussive headache [62]. As mentioned previously, dissection, cerebral venous thromboses, and CSF leaks with resulting intracranial hypotension should be considered in the differential for a headache following closed head injury and trauma.

Third Ventricular Colloid Cyst

Colloid cysts are benign congenital cysts that arise in the anterior third ventricle (Fig. 1.8). They are usually asymptomatic, and found

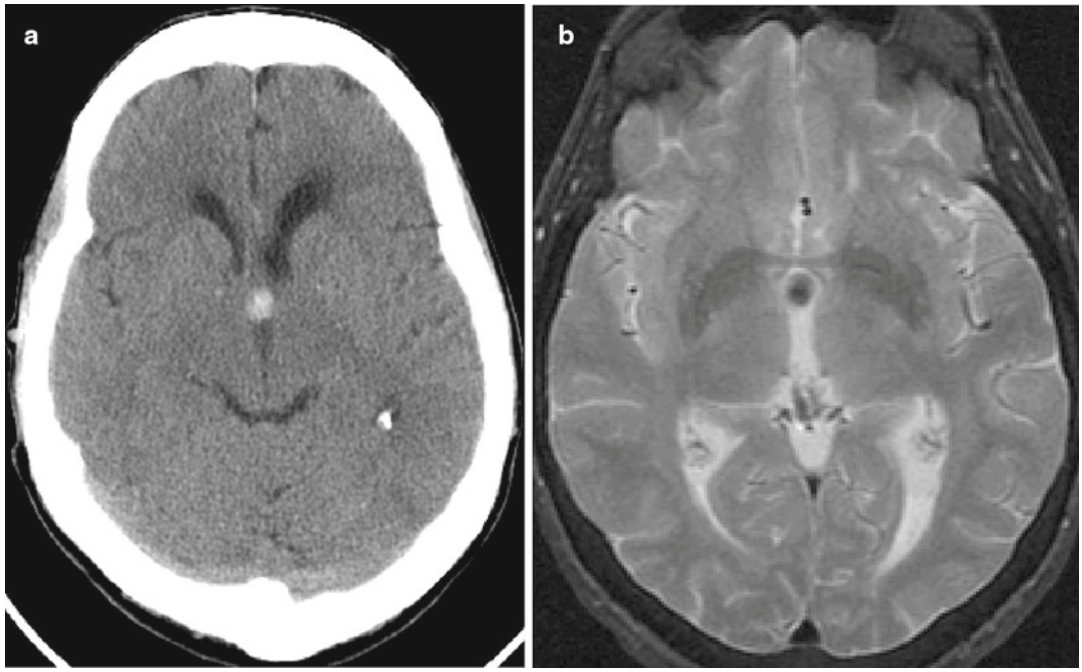

Fig. 1.8 Colloid cyst. Unenhanced CT (**a**) shows a hyperdense lesion anterior to the third ventricle that is seen as a low-signal lesion on T2-weighted MRI (**b**)

incidentally on imaging in adulthood. However, if the cyst obstructs the foramen of Monro it can disrupt CSF flow and lead to hydrocephalus. If both foramen of Monro are obstructed, this may lead to syncope, coma, or death. Occasionally, the tumor will act as a ball valve and only intermittently obstruct CSF flow. When this happens, the patient may complain of a severe positional headache, relieved in recumbency, sometimes associated with nausea and vomiting [63, 64].

Trigeminal Neuralgia

Classic trigeminal neuralgia presents as paroxysmal attacks of intense, sharp, and stabbing pain along one or more divisions of the trigeminal nerve. These attacks last from less than 1 s to 2 min, and are often precipitated by stimulating certain "trigger zones." Chewing, talking, brushing teeth, cold air, or the slightest touch may trigger the paroxysmal pain [1]. Trigeminal neuralgia is most commonly due to compression of the trigeminal nerve by a blood vessel near its origin where it exits the brainstem. A demyelinating lesion or infarct at this so-called dorsal root entry zone may also cause trigeminal neuralgia, and should be suspected in younger patients presenting with these symptoms. Much less commonly trigeminal neuralgia is due to compression by a mass lesion such as a meningioma or schwannoma, or is idiopathic. Imaging is frequently performed to rule out a secondary etiology, but usually in an outpatient, rather than emergent, setting.

Glaucoma

Acute-angle glaucoma may present with headache and associated eye discomfort, and there are also reports of subacute angle-closure glaucoma presenting with headache as the main presenting complaint [65]. If not identified and managed properly, either of these can result in permanent vision loss in the affected eye. Be concerned about glaucoma if the patient's headache pain came on suddenly when exposed to the dark. When going from light to dark, the sudden dilation of the pupil

may block the outflow channels in the anterior chamber, leading to sudden increased intraocular pressure. The patient may complain of sudden severe unilateral headache and eye discomfort, associated with blurred vision in the affected eye and "halos" around lights. The affected eye is often red with a middilated, sluggishly reactive pupil (may be irregularly shaped) and a hazy cornea [66]. Nausea and vomiting may be present. This is best evaluated by an emergent ophthalmology consult.

General Approach to the Management of Primary Headache in the Emergency Department

Once secondary headache disorders are excluded, the primary goal of the treating physician is to provide relief of headache pain and the accompanying symptoms such as nausea and vomiting. The majority of patients who present to the ED with headache will be diagnosed with a severe and/or prolonged migraine attack. Occasionally, patients with other diagnoses such as tension-type or cluster headache will present to the emergency department. Often the individual will have utilized her/his usual headache remedies without success. If the attack has lasted hours or longer and has been accompanied by poor oral intake of fluids with or without vomiting, the patient will likely be fluid depleted. If the patient is dehydrated, intravenous fluids need to be administered along with pharmacologic agents that treat the pain and other manifestations that accompany the pain. Often patients are quite distressed and anxious due to the duration and/or severity of the attack. The following general principles should be utilized:

- Place the patient in a darkened, quiet room.
- Provide reassurance.
- Provide IV rehydration.
- Treat nausea and vomiting quickly.
- Implement treatment with non-oral medication as soon as possible.
- Do not restrict antiemetics in patients with nausea, as many of the agents in this class are dopaminergic antagonists which have an antimigraine action in addition to their antiemetic effect.
- Avoid drug-dependency-producing agents when possible (avoid butalbital and limit opioids, or at least use opioids with care).
- Rather than minimal dosing, use medication doses that are likely to be most effective.
- Use "migraine-specific" therapy when possible.
- Educate the patient regarding his condition.
- The patient should be counseled to make arrangements for follow-up as an outpatient for consideration of approaches that will optimally manage headaches.

Protocols for Acute Treatment of Migraine in the Emergency Department

There are several protocols employing a variety of agents that can be utilized for management of primary headache disorders in the emergency department. Again, most patients will be presenting with migraine and most of the protocols have been developed specifically for this disorder. Several of these have been shown to be effective in small prospective, controlled trials. To address the severe headaches that lead patients to seek care in the emergency department, many of these protocols focus on parenteral agents. Obviously, the treating care provider may elect to use an oral agent for management that can be self-administered by the patient.

The medications fall into relatively few categories of agents: (1) migraine-specific drugs (dihydroergotamine and sumatriptan); (2) dopamine (D_2)-blocking agents, such as neuroleptic drugs and metoclopramide; (3) other non-dependency-producing medications; and (4) opioid drugs.

It is important to note that drugs from different classes are often used together. This is done to maximize efficacy, to treat symptoms other than pain (e.g., nausea and vomiting), and, in some cases, to reduce the likelihood of side effects of another agent. For example, D_2 antagonists are always administered with intravenous dihydroergotamine to minimize its side effects of nausea and vomiting.

Migraine-Specific Agents

Sumatriptan (5HT 1B/D Receptor Agonist)

Sumatriptan, 4 or 6 mg injected subcutaneously, has been shown to be both efficacious for treatment of acute migraine headache and for associated symptoms [67]. The dose can be repeated after an hour. Response rate at 1 h after a single dose of 6 mg is 70% [68]. Side effects include chest tightness, tingling, flushing, dizziness, and limb heaviness. Sumatriptan is the triptan of choice in the emergency department because it is the only triptan available in a subcutaneous formulation, which provides a rapid serum concentration and bypasses nausea, vomiting, and gastroparesis. Sumatriptan is at this time the only triptan to be considered "compatible" with breastfeeding by the American Academy of Pediatrics.

Contraindications for sumatriptan include:

- Pregnancy (relative contraindication)
- History or suspicion of ischemic heart disease
- History of coronary artery disease or Prinzmetal's angina
- Severe peripheral vascular disease
- Use of an ergot alkaloid (i.e. DHE, ergotamine) or other 5HT 1 agonist (i.e. another triptan) within 24 h
- Uncontrolled hypertension
- Previous adverse reaction
- Basilar or hemiplegic migraine
- Ischemic cerebrovascular disease

Dihydroergotamine

Dihydroergotamine mesylate (DHE) is an effective parenteral treatment for migraine attacks. The beneficial effects of DHE were initially attributed to vasoconstriction, but other mechanisms involving neurogenic inflammation and activity within central serotonergic systems provide a better explanation [69, 70]. It is important to note that headache resolution after treatment with IV DHE and metoclopramide has been reported in patients suffering headaches secondary to viral or carcinomatous meningitis; thus, response does not imply the diagnosis of a primary headache such as migraine or cluster headache [71]. Common side effects of DHE are nausea, vomiting, diarrhea, abdominal cramps, and leg pain.

DHE may be administered subcutaneously, intramuscularly, or intravenously. The intravenous route is the most rapidly effective. Unfortunately, the side effects of nausea and vomiting seem to be more prominent with intravenous administration.

The usual dose when administered subcutaneously or intramuscularly is 1.0 mg [72, 73]. In order to help prevent nausea, give an antiemetic such as 10 mg IV metoclopramide or 10 mg IV prochlorperazine approximately 10 minutes before giving DHE intravenously. The side-effects and the utility of these D_2 blocking agents are outlined elsewhere in this chapter. DHE, 0.5 mg, is then slowly administered over a few minutes [74–76]. An additional 0.5 mg dose may be administered a few minutes later if no significant nausea or chest pain has developed. A one mg dose via subcutaneous, intramuscular, or intravenous routes may be repeated after one hour. In the case of status migrainosus or truly intractable migraine, the patient may require hospital admission, and could be treated with repetitive or continuous DHE, using published protocols such as those of Raskin or Ford [77–79]. For instance, if the patient tolerates the medicine, IV DHE could be given as 0.5, 0.75, or 1.0 mg every 8 hrs for 2–5 days along with an antiemetic such as metoclopramide 10 mg IV every 8 hours. Please see (Fig. 1.9) for an example protocol. If extrapyramidal symptoms such as dystonia, akathisia, or oculogyric crisis develop from the metoclopramide, these could be addressed using parenteral benztropine mesylate or diphenhydramine. Alternatively, parenteral benztropine mesylate or diphenhydramine could be given with as a pretreatment with each dose of DHE/metoclopramide to prevent these extrapyramidal side effects.

Contradictions for DHE include:

- Uncontrolled hypertension
- Ischemic heart disease
- Vasospastic angina
- Severe peripheral vascular disease
- MAO inhibitors within the last 2 weeks
- Prior use of a triptan within the last 24 h
- Significant hepatic disease
- Pregnancy
- Hemiplegic or basilar artery-type migraine

Antidopaminergic Agents

Antidopaminergic agents have well-recognized antiemetic and sedative effects which prove useful

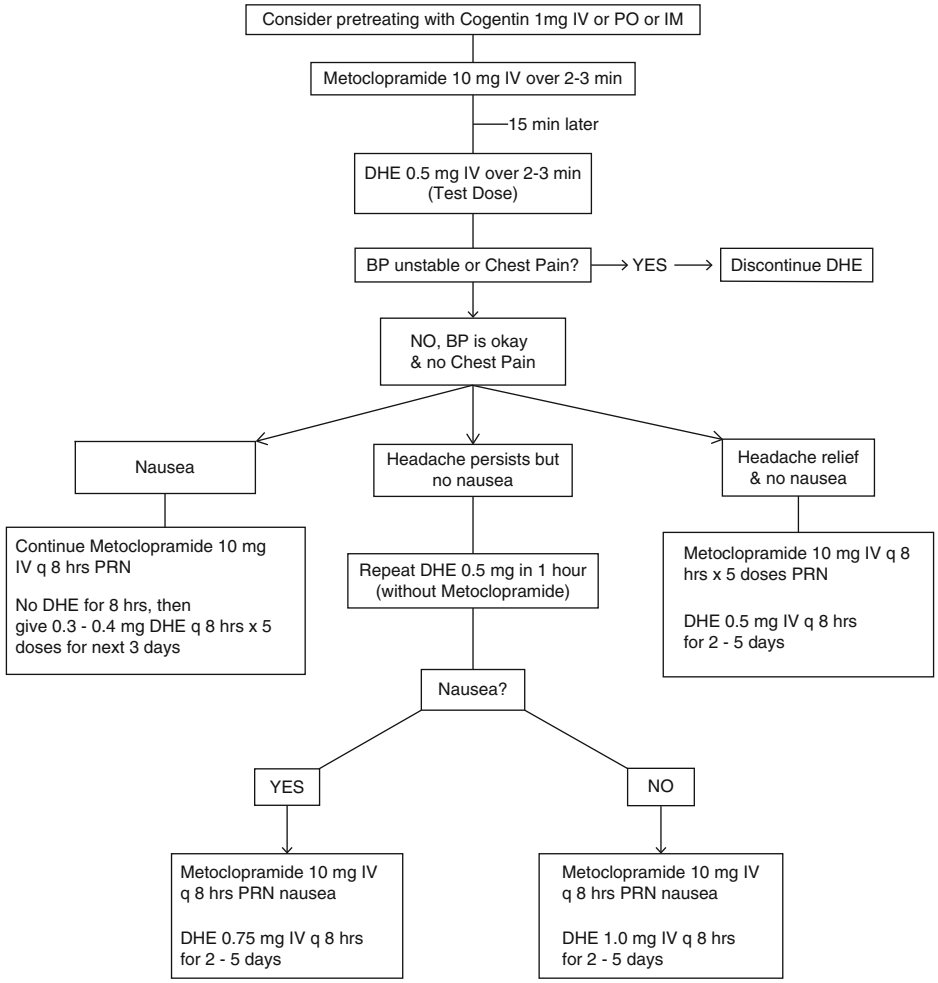

Fig. 1.9 Repetitive (every 8 hours) intravenous (IV) dihydroergotamine mesylate (DHE)–Raskin protocol. PO, Orally; IM, intramuscular; BP, blood pressure; PRN, as needed; q, every. (Used with permission from Seminars of Neurology…..blah blah blah…. Adapted from Raskin31; presented at: Headaches in the ED; AAN Annual Meeting; May 4, 2007; Boston, MA.)

in the treatment of acute headache. In addition, there is significant clinical and experimental data suggesting that there is relative hyperactivity of dopaminergic neurotransmission in at least some migraineurs. These agents may have a specific antimigraine effect via blockade of D_2 dopamine receptors [80].

Common acute side effects of these agents include akathisia, acute dystonia, dizziness, and somnolence. Prolonged exposure (which is not an issue in the emergency department setting) may result in drug-induced tardive dystonia, parkinsonism, and tardive dyskinesia. The dizziness may be due to hypotension; therefore, carefully monitoring of vital signs, including a standing blood pressure prior to discharge, should be routine after administration of these agents.

The acute extrapyramidal side effects can be ameliorated by diphenhydramine, 25 mg, (intravenously or intramuscularly) or benztropine, 1 mg (intravenously or intramuscularly).

Rare but potentially fatal complications of these drugs include prolonged QT syndrome and *torsades de pointes*. Some individuals have an underlying genetic predisposition to the disorder, but it can also be acquired secondary to pharmacologic

agents. For a list of agents which may produce a prolonged QT interval, see the online resource at Arizona Center for Education and Research on Therapeutics [79]. If a patient is taking one of these agents, treatment with a D_2 agent should be used with care. Prior to the parenteral administration of any of these agents, it is suggested that an ECG be obtained and the QT interval be carefully measured. If there is evidence of a prolonged QT interval, these agents should not be used.

Controlled trials show that a number of these drugs are effective in the acute management of migraine headache.

Prochlorperazine

Prochlorperazine has been shown to be an effective pain-abortive agent that can be used in repeated intravenous doses in a hospital or emergency department setting [80, 81]. Prochlorperazine, 10 mg per cc, can be diluted with 4 cc of normal saline to the concentration of 2 mg per cc. This is injected at a rate of 1 mg/min until the headache is relieved, or a maximum of 10 mg is administered [82, 83]. Most often, a dose of 10 mg of intravenous prochlorperazine is injected over 2–5 min and this is repeated every 20 min, up to a maximum dose of 30 mg. Prochlorperazine, administered as a 25-mg rectal suppository, is also effective for acute migraine therapy [84]. Its onset of action, however, is substantially slower than when administered intravenously.

Chlorpromazine

A number of studies demonstrate that chlorpromazine is an effective parenteral, acute treatment for migraine attacks. Prior to intravenous administration of this agent, the patient is often pretreated with 500 ml of normal saline to reduce the hypotensive side effect; more fluid may be appropriate if the patient has been vomiting or is dehydrated.

One of the most effective and easiest to use protocols is 12.5-mg chlorpromazine IV, which is repeated at 20-min intervals to a maximum of 37.5 mg [85]. Another protocol consists of chlorpromazine 0.1 mg/kg IV, which is repeated every 15 min as needed, up to a total of three doses [86]. Alternatively, chlorpromazine, 25 mg per cc, is diluted with 4 cc of normal saline to a concentration of 5 mg per cc. To reduce the risk of hypotension, chlorpromazine can be administered at a rate of 5 mg (1 cc) every 5 min until the headache is relieved, or the entire 25 mg is administered. An additional 10 mg (for a total of 35 mg) may be given in some cases. Chlorpromazine, 1 mg/kg intramuscularly, is also an effective headache-abortive treatment, but its action is slower in onset and the efficacy is less than by intravenous administration [87, 88]. Bigal et al. performed a double-blind randomized controlled study of 128 tension-type headache sufferers who either received placebo or 0.1 mg/kg of chlorpromazine IV as a one-time dose [89]. At 60 min, effects were statistically different from placebo for pain, nausea, photophobia, phonophobia, and need for rescue medication. Side effects included drowsiness and postural hypotension.

Haloperidol

In a small open study, haloperidol, 5 mg IV over a few minutes, resulted in headache relief [90]. A more recent randomized, controlled trial found that 5 mg of haloperidol in 500 cc of normal saline as a 20–30-min one-time infusion resulted in 16/20 (80%) of patients enjoying a marked relief from pain (a drop of greater than three on the visual analog pain scale) versus 15% in the placebo group measured between 1 and 3 h after infusion [91]. Side effects included 53% motor agitation (akathisia) and 53% sedation. Three of 20 patients treated with haloperidol returned to the emergency department with recurrent headache within 2–3 days. Haloperidol seems to cause less sedation and less hypotension than prochlorperazine or chlorpromazine.

Droperidol

Droperidol can be administered as 2.5 mg intravenously over 1 min, and may be repeated every 30 min, up to a total of 7.5 mg [92]. Droperidol can also be effective when administered via the intramuscular route in doses ranging from 2.75 to 8.25 mg [93]. Though randomized controlled studies have demonstrated an effect equal to prochlorperazine, there is now a black-box warning for droperidol because it may provoke QT interval prolongation, *torsades de pointes*, or cardiac arrest.

ECG monitoring should occur before, during, and for up to 2–4 h after administration, especially for those with congestive heart failure, bradycardia, cardiac hypertrophy, hypokalemia, hypomagnesemia, or those patients using diuretics or other drugs known to cause QT interval prolongation [94]. As already noted, QT prolongation is a risk of all drugs in this class.

Metoclopramide

Metoclopramide, while not a neuroleptic agent, does have D_2 dopamine receptor-blocking properties [78]. It can be administered in a dose of 10 mg intravenously over a few minutes [95, 96]. Metoclopramide is generally less effective than the above neuroleptic agents, but efficacy can be substantially enhanced when used in combination with other antimigraine agents [97].

Sodium Valproate

Several preliminary or open-label studies found intravenous sodium valproate to be an effective, well-tolerated, acute abortive agent for migraine in the emergency setting [98, 99]. Sodium valproate, 300–500 mg diluted in 100 cc of normal saline, is infused at a rate of 20 mg/min. Intravenous valproate has several advantages including lack of cardiovascular side effects (no telemetry required), no interaction with triptans or ergot alkaloids, lack of sedation, and absence of dependence or habituation. Trials have used various dosing regimens. The half-life is 9–16 h, bioavailability is approximately 100%, and therapeutic blood levels are reached almost immediately [100].

In an open-label trial, Mathew et al. used 300-mg IV sodium valproate in 61 migraineurs and found that 73% of attacks had significant improvement within 30 min [99].

An open-label comparison between intravenous valproate 500 mg versus 10-mg IM metoclopramide followed by IM DHE 1.0 mg found that both worked equally well and valproate had fewer side effects [98].

A randomized, controlled study comparing intravenous valproate (500 mg) with IV prochlorperazine (10 mg) over 2 min found that prochlorperazine was statistically and clinically superior to IV valproate in reducing pain and nausea in migraine patients [101].

Another open-label trial of intravenous valproate in doses ranging from 300 to 1,200 mg applied to a mixture of headache types found that 63% had at least a 50% reduction in pain intensity and only two people had dizziness [102]. It should be avoided in patients with hepatic disease. It is contraindicated in pregnancy; thus, women of childbearing age should have a negative pregnancy test before administration. Controlled trials need to be performed to confirm the efficacy of this agent.

Magnesium Sulfate

The evidence for magnesium sulfate's efficacy is far from overwhelming, but it can be used safely during pregnancy. One study concluded that 1 g of magnesium sulfate, given intravenously, resolved or improved acute migraine headaches (as well as cluster headaches) [103]. Improvement was more likely if basal serum ionized magnesium levels were low (less than 0.70 mmol/L). These results have not been confirmed in a placebo-controlled study. In this trial, magnesium sulfate had no significant side effects except mild flushing.

A recent study of 113 migraineurs compared 10-mg intravenous metoclopramide versus 2-g intravenous magnesium sulfate versus placebo. The study measured pain reduction at 30 min and found no difference compared to placebo for either magnesium or metoclopramide [104]. Another study found magnesium to be moderately helpful, but not as effective as prochlorperazine [81]. Yet another study showed that magnesium sulfate (1-g IV) was no better than placebo in pain relief when all patients with migraine were analyzed. However, in migraine with aura, there was significant improvement of pain and of all associated symptoms compared with controls with a therapeutic gain of nearly 37% at 1 h [105].

Nonsteroidal Analgesics

Analgesics are widely used for acute treatment of headache. Ketoralac, a nonsteroidal anti-inflammatory drug which is available for injection, can be useful for treatment of some migraine attacks. The medication is given in a 30–60-mg IM injection [77]. Intravenous ketorolac (0.4 mg/kg) can

terminate both headache- and migraine-associated allodynia in up to 68% of patients within 1 h of treatment, even in those patients who have failed to respond to sumatriptan [106]. Ketorolac at a dose of 30-mg IV was beneficial but not as effective in reducing pain as 10-mg IV prochlorperazine [107]. Most patients should also be treated with an antiemetic. Drowsiness, dyspepsia, and nausea are potential side effects. Acute renal failure and gastrointestinal hemorrhage have been precipitated rarely by this agent.

In a small study comparing ketorolac 60-mg IM versus IV DHE/metoclopramide in various doses, only six of nine patients had moderate relief with ketorolac versus eight of nine who were given DHE/metoclopramide [77].

Corticosteroids

Corticosteroids are typically given in combination with other antimigraine agents to enhance efficacy. Dexamethasone can be given IV or IM. Doses as high as 10–20-mg IV given over 10 min, followed by 4-mg IV every 6 h as needed, are very effective [108–110]. Alternatively, a one-time IM injection of 8 mg can also be employed [111].

A meta-analysis of studies that evaluated the efficacy of dexamethasone in addition to other therapy for acute migraine was performed. The analysis included studies that used randomized, double-blind, placebo-controlled methodology and that were performed in the emergency department. A pooled analysis of seven trials involving 742 patients suggested a modest but significant benefit when dexamethasone was added to standard antimigraine therapy. The analysis showed the addition of dexamethasone reduced the rate of patients with moderate or severe headache on 24- to 72-h follow-up evaluation (RR of 0.87, 95% CI of 0.80–0.95; absolute risk reduction of 9.7%). The treatment of 1,000 patients with acute migraine headache using dexamethasone in addition to standard antimigraine therapy would be expected to prevent 97 patients from experiencing the outcome of moderate or severe headache at 24–72 h after emergency department evaluation [112].

Opioids

Despite multiple effective regimens of nonopioid medications, opioids continue to be commonly used for acute management of headache in the emergency department. In a nationwide survey of 811,419 adult migraine sufferers who visited an emergency department, 51% were treated with opioids and an alarming 77% of these had not received any nonopioid medications as a first-line attempt [113]. In a Canadian survey of 500 emergency department visits for headache, 59.6% of patients received narcotics as first-line treatment [114]. Opioids are not "migraine specific," and are generally not as effective as other agents. Further, in the setting of frequent emergency department or outpatient visits, their use raises concern about rebound and tolerance. Nevertheless, there are some patients for whom an opioid is the most effective and best-tolerated agent for acute, severe headaches, and opioids continue to play a role as rescue agents. Meperidine is the most commonly utilized agent in this setting. It may be administered intravenously or intramuscularly, most commonly in a dose of 75–150 mg. It should be accompanied by promethazine, 25–50 mg, or hydroxyzine, 25–100 mg, intramuscularly to treat nausea and vomiting; these also provide sedative and anxiolytic effects [115].

Because clinical trials assessing efficacy and side effects of meperidine performed to date have been small and have not arrived at consistent conclusions, Friedman et al. performed a systematic review and meta-analysis to determine the relative efficacy and adverse effect profile of opioids compared with nonopioid active comparators for the treatment of acute migraine [116]. Four trials (involving 254 patients) compared meperidine to dihydroergotamine, four trials (involving 248 patients) compared meperidine to an antiemetic, and three trials (involving 123 patients) compared meperidine to ketorolac. Meperidine was less effective than dihydroergotamine at providing headache relief (OR of 0.30; 95% confidence interval [CI] 0.09–0.97) and trended toward less efficacy than the antiemetics (OR of 0.46; 95% CI 0.19–1.11); however, the efficacy of meperidine was similar to that of

ketorolac (OR of 1.75; 95% CI 0.84–3.61). Compared to dihydroergotamine, meperidine caused more sedation (OR of 3.52; 95% CI 0.87–14.19) and dizziness (OR of 8.67; 95% CI 2.66–28.23). Compared to the antiemetics, meperidine caused less akathisia (OR of 0.10; 95% CI 0.02–0.57). Meperidine and ketorolac use resulted in similar rates of gastrointestinal adverse effects (OR of 1.27; 95% CI 0.31–5.15) and sedation (OR of 1.70; 95% CI 0.23–12.72). The authors appropriately conclude that emergency department physicians should consider alternate parenteral treatments for migraine headaches.

Indeed, meperidine is losing favor among pain specialists for use as an analgesic and many authorities argue that other opioids should be used for acute pain. This is due to meperidine's poor efficacy, toxicity, and multiple drug interactions [117]. The argument can be made that if a parenteral opioid is needed, then an opioid other than meperidine should be selected and administered in an equipotent dose [118].

Cluster Headache Treatment

Therapeutic options for cluster headache vary in some respects from other primary headache disorders and are therefore considered separately. Effective treatments include:

Oxygen

A range of 8–12 L/min of 100% oxygen through a closed face mask can abort most cluster headache attacks if the sufferer can begin therapy at the onset of the attack. Sometimes, a flow rate of 15 L/min is effective when lower flow rates are not. Oxygen's effectiveness in cluster headache has been proven in a double-blind controlled trial [119].

Sumatriptan

In one study, 96% of cluster headache sufferers achieved pain relief in 15 min with 6-mg SC sumatriptan [120]. The maximal recommended dose per 24 h is 12 mg. Now that it comes in a 4-mg subcutaneous dosage, a cluster patient may use up to three doses a day. Some may break open the subcutaneous device and dole out only small quantities in order to make their medicine last longer and treat more attacks.

Dihydroergotamine

One milligram IV dihydroergotamine preceded by 10-mg metoclopramide can rapidly abort cluster headache attacks in less than 15 min [121]. Subcutaneous or IM injections of 1-mg DHE up to 2–3 times a day can be used outside of the office or emergency department, but onset of relief is slower. Intranasal DHE is difficult to use and too slow to abort individual attacks, but it may lessen attack severity.

Corticosteroids

Corticosteroids can provide a temporary reprieve lasting days to weeks in many patients with cluster headache. Corticosteroids have been used to treat cluster headache for over 50 years, and they have been shown to be more effective than placebo [122]. In a large, retrospective series, Kudrow found that 60 mg a day produced a complete remission in up to 77% of patients [123].

In one open-label study, 13 cluster headache patients used 30 mg/kg of IV methylprednisolone as a 3-h infusion in saline on the eighth day of the cluster period [124]. Only 3 of 13 patients had a complete remission of headache, and the mean interval until the next attack was 2–7 days indicating no advantage over prednisone.

In another study using IV methylprednisolone, 250-mg boluses over three consecutive days, followed by 90 mg per day of oral prednisone tapered off over 4 weeks, lowered attack frequency substantially for several weeks [125].

Special Circumstance: Treatment of Headache in the Pregnant Patient

Because home treatment options are somewhat limited, the pregnant migraine sufferer may be forced to come to the emergency department for management. There is general agreement that Tylenol, possibly combined with caffeine, is a good first-line choice for the acute migraine attack [23, 24, 126, 127], as both are felt to be

generally safe during pregnancy. The drawback to Tylenol is that it is a short-acting analgesic and, if taken too frequently, could contribute to a potential rebound, or analgesic overuse, headache. Furthermore, by the time the patient arrives to the emergency department, there is a strong possibility that she has already tried this.

As mentioned early in the section on headache management, the initial approach should include conservative measures, such as making sure the patient is well hydrated. Magnesium sulfate is considered safe for the fetus and may help with the migraine [128]. Ibuprofen and naproxen are generally considered safe during the second trimester, but should be avoided during the third trimester as they may cause premature closure of the ductus arteriosus [24, 129]. Some studies have shown a small risk of increased spontaneous abortion and congenital malformations when these NSAIDs are taken in the first trimester, so one might also be cautious early in pregnancy [130].

For nausea, metoclopramide has been used during all stages of pregnancy with no evidence of embryo, fetal, or newborn harm, and is considered FDA class B (no evidence of risk in humans, but no controlled studies) [130]. Other antiemetics such as prochlorperazine remain class C due to limited information, and therefore should be reserved for when the benefits are thought to outweigh the potential risks [129, 130].

As mentioned previously, narcotic medications should be avoided if at all possible, given the association with drug dependency and rebound headache. With prolonged use in pregnancy, especially in the third trimester, there is a risk of neonatal addiction and respiratory distress. Of the opiate medications, codeine has been associated with more reports of cleft lip/palate, cardiac, and respiratory defects and should therefore probably be avoided, especially during the first trimester [131]. Morphine, oxycodone, and meperidine are probably not teratogenic, but the data is somewhat limited [130]. Given the limited options during pregnancy, these may be considered for very short-term use, during status migrainosus, if necessary.

Sumatriptan was embryolethal in rabbits when given in large doses intravenously, and produced some vascular and skeletal anomalies when given in large doses orally [130]. The data in human fetuses is less clear. In the sumatriptan pregnancy registry, sumatriptan use has been associated with an increased risk of preterm delivery and low birth weight [132]. There have also been a small number of recorded birth defects, with any-trimester exposure proportion of 4.4% (95% CI 2.8–6.8%) as compared to the prevalence of birth defects in migraineurs, which has been estimated at 3.4% [130]. In other retrospective and observational cohort studies, the risk has been even less [130]. Ultimately, there is not enough data on sumatriptan use in human fetuses to detect minor anomalies. Furthermore, some of the existing studies lack the long-term follow-up needed to detect late adverse effects. As there is insufficient data to rule out risk to the fetus, all triptans including sumatriptan remain FDA pregnancy class C.

Corticosteroids have been shown to increase major malformations when used in the first trimester. Therefore for the first trimester, they are FDA class D [130], showing positive risk to humans. One of these risks appears to be a small risk of orofacial defects [130]. For the rest of the pregnancy, animal studies show clear risk to the fetus, but the human studies are less clear. Because of the limited information, they are considered FDA class C during second and third trimesters. Of the corticosteroids, oral prednisone seems to have less risk than prednisolone [130], and has been advocated by some as an option for the short-term management of status migrainosus [23, 129].

Ergotamine/DHE should be avoided during pregnancy (FDA class X) as there have been idiosyncratic responses to treatment that have been associated with fetal toxicity and teratogenicity, possibly due to the disruption of maternal-fetal vascular supply [130]. Valproic acid (FDA class D, human data suggests risk) is also a known teratogen, and should be avoided during pregnancy [130].

Summary of pregnancy list in the acute setting [24, 129, 130]:

- *Probably safe in the acute setting (FDA class B)*: Tylenol, caffeine, magnesium, NSAIDs during the second trimester, metoclopramide, morphine, oxycodone, and meperidine
- *Use if the benefit outweighs the risk (FDA class C)*: NSAIDs during first trimester, triptans, prochlorperazine, oral prednisone, and codeine
- *Probably avoid (FDA class C but shows risk during first and third semesters)*: Aspirin
- *Avoid (FDA class D or X)*: NSAIDs or aspirin during third trimester, sodium valproate, and ergotamine/DHE

Because of the difficulty in management, the pregnant patient should receive counseling on how to minimize the frequency of future headaches. This would include avoidance of headache triggers and maintaining regular meals and sleep patterns. Physical therapy, exercise, relaxation, and biofeedback are nonmedication options to try. Thermal biofeedback, in particular, has been associated with headache reduction during pregnancy [129].

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Low Back Pain Emergencies

2

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Abstract

Low back pain (LBP) is exceedingly common. Most patients with LBP present acutely or subacutely. The clinician is frequently faced with the task of determining whether or not the individual LBP patient has an emergent or soon-to-be-emergent underlying condition. The approach to the patient with acute or subacute LBP includes a search for red flags in the history and careful physical and neurological examinations that can indicate the likelihood of an underlying urgent or emergent condition. In the absence of red flags, patients can be treated conservatively for 1 month or more without diagnostic testing.

Patients who have or develop red flags should undergo urgent and sometimes emergent investigation. LBP emergencies include infections (vertebral osteomyelitis and/or epidural abscess), primary and metastatic spine tumors, thoracic aortic dissection (TAD), expansion or rupture of an abdominal aortic aneurysm (AAA), a large lumbar disk protrusion or extrusion with compression of the cauda equina, and thoracolumbar fractures.

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Introduction

Low back pain (LBP) is defined as pain located between the lower rib cage and the gluteal folds, often extending or radiating into the thigh (between the hip and knee) and/or leg (between the knee and ankle) [1]. Acute LBP usually lasts less than 3 months [2]. It is one of the most common medical problems in the adult population [1, 2]. LBP is the second leading reason for visiting a primary care physician in the USA [3] and the second most common reason for frequent utilization of emergency department services [4]. It is estimated that up to 90% of adults will experience LBP at some time in their lives [5], and LBP is the most common cause of back and spine disability among young and middle-aged people [6].

LBP represents a substantial socioeconomic challenge. Frymoyer and Cats-Baril estimated the total cost of low back disorders in 1990 to be in the range of $50–100 billion per year [7]. Katz reviewed this data and suggested that the total annual cost of LBP was $100–200 billion in 2005 [8]. Socioeconomic effects of a medical condition include direct and indirect costs. Direct costs are the costs related to diagnosis and medical management of the condition (e.g., tests, treatments, hospitalization, office visits, and alternative therapies). Indirect costs are the resources expended to address disability associated with the condition (e.g., lost wages, reduced productivity, compensation payments, and additional caregiving expenses) [8]. About two-thirds of the total costs of LBP are indirect [8]. Because indirect costs are typically dependent on change in work status, they are difficult to estimate for adults who are outside the workforce (e.g., unemployed, retired, students, and individuals disabled by other conditions). About 5% of Americans miss at least 1 day of work per year due to LBP [8, 9].

In a randomly selected group of 2,809 adults obtained from a cross-sectional telephone survey of North Carolina households, 26% reported impairing chronic LBP [10]. Eighty-four percent of those with chronic back pain had at least one visit to a health-care provider in the previous year, almost half of whom saw an orthopedic or neurologic surgeon. Those who sought care had LBP for a mean of 9.8 years, had a mean age of 53 years, and 62% were women [10]. Forty-six percent of the patients with chronic LBP received plain radiographs in the preceding year, and 36% underwent a computed tomography (CT) scan or magnetic resonance imaging (MRI), half of whom received a second advanced imaging study within the year of reporting [10].

Although most low back disorders do not present as emergencies, recognition of those that do is critical to good outcomes. This chapter will focus on the evaluation and treatment of LBP emergencies. The critical elements from the medical history and physical and neurological examinations will be identified for determining the etiology and directing appropriate use of ancillary studies, such as plain X-rays, CT, MRI, and medical and surgical consultations. Treatment for the serious causes of LBP will be addressed.

Epidemiology

The interpretation of epidemiologic studies of LBP can be confusing, mostly due to the use of different definitions for back pain, disparities in

the ages of the populations studied, and physical and socioeconomic factors which could contribute to the development of back pain or influence symptoms [2].

The incidence of LBP varies between studies [11, 12]. In a population-based, prospective cohort study of 308 patients free of LBP for 6 months, Cassidy et al. reported a cumulative incidence of LBP in 18.7% in the subsequent year [11]. Most of the cases were mild and no differences were found between genders or across age groups. In a prospective epidemiological survey of 2,715 adults free of LBP in the prior month, Papageorgiou found that the 1-year cumulative incidence of new episodes of LBP for which evaluation was sought was 5% for women and 3% for men. However, 31.5% of the patients reported a new episode of LBP for which no evaluation was sought. Patients with a history of LBP in the past had twice the rate of new episodes compared to those with no past history of LBP [12].

How often do patients present with a more serious pathology underlying their acute back pain? Winters et al. estimated that 5–10% of patients have underlying life-threatening problems, such as vascular catastrophes, malignancy, spinal cord compressive syndromes, and infectious diseases [13]. Deyo et al. estimated that in primary care, about 4% of patients with back pain will have compression fractures, 3% have spondylolisthesis (which can be and is often an incidental finding), 0.7% have spinal malignant neoplasms, 0.3% have ankylosing spondylitis, and 0.01% have spinal infection [14]. In contrast to these estimates, Henschke et al. reported the prevalence of serious spinal pathology in 1,172 consecutive patients receiving primary care for acute LBP from primary care clinics in Sydney, Australia [15]. There were only 11 cases (0.9%) of serious pathology, eight of whom had fractures [15]. The likelihood of finding serious underlying pathology in the patient with acute LBP will depend upon where they are seen (the likelihood of serious disease is higher in the emergency department compared to the outpatient clinic) and their presentation, including the presence of red flags.

Clinical Features and Evaluation

The evaluation and diagnosis of back pain is a challenge. Although most cases are presumed to be of musculoskeletal origin and benign, as noted, back pain can be caused by serious life-threatening conditions [16]. Approximately 85% of patients with isolated back pain cannot be given a precise pathoanatomical diagnosis [17].

The patient's history and findings from the physical and neurological examinations can be very helpful in determining the cause of a patient's back pain. Because an exact diagnosis is not possible in many patients, Deyo recommends answering these three questions (1) Is a systemic disease causing the pain? (2) Is there social or psychological distress that may amplify or prolong the pain? (3) Is there neurological compromise that may require surgical evaluation [17]? Careful history taking and physical and neurological examinations are needed to answer these questions and determine the cause of an individual patient's LBP. The role of the physician in the initial evaluation is to identify key elements or red flags that can indicate the possibility of significant spinal and nonspinal pathology. The presence of these indicators will help guide further diagnostic workup and their absence can rule out the need for additional tests during the first 4 weeks of symptoms, since spontaneous recovery is expected within 1 month in 90% of patients lacking red flags [18].

Clinical practice guidelines from the US Agency for Health Care Policy and Research (AHCPR now known as the Agency for Healthcare Research and Quality or AHRQ at http://www.ahrq.gov) and the Institute for Clinical Systems Improvement (at http://www.icsi.org) have determined a list of red flags that should be sought in patients with LBP (Table 2.1). The red flags raise a suspicion of serious underlying spinal conditions such as fracture, tumor, infection, and/or severe neurological deficits including the cauda equina syndrome. It is recommended that clinicians evaluating patients with acute or worsening LBP routinely inquire about these red flags.

Table 2.1 Red flags for potentially serious underlying cause of low back pain

Red flag item	Description	Rationale
Trauma	History of major trauma (e.g., motor vehicle accident, fall from height) or minor trauma in the setting of possible osteoporosis	Possible fracture, especially in an older or osteoporotic patient
Age	More than 50 years or less than 20 years	Increased risk of tumor, abdominal aortic aneurysm, fracture, infection
History of cancer	Past or present history of any type of cancer	History of cancer increases risk of back pain caused by metastatic tumors arising from the lung, breast, kidney, prostate, others
Fever, chills, night sweats	Oral temperature ≥37.8°C (100°F), chills, sweats, temperature changes at night	Constitutional symptoms increase risk of infection or cancer
Weight loss	Unexplained weight loss >4.5 kg (10 lbs) in 3 months, not directly related to a change in activity or diet	May indicate cancer or infection
Recent infection	Recent bacterial infection such as a urinary tract infection	Increases risk of infection
Immunosuppression	Immunosuppression for any reason (e.g., transplant, steroid use, IV drug abuse, HIV)	Increases risk of infection
Recumbency or night pain	Pain that is worsened by recumbency or awakens the patient from sleep, unrelated to movement or positioning	Increases risk of cancer, infection, or an abdominal aortic aneurysm
Saddle numbness	Reduced sensation in the second–fifth sacral dermatomes (perianal region)	May indicate cauda equina syndrome
Bladder or bowel dysfunction	Urinary retention, increased frequency of urination, incontinence of urine or stool, dysuria, hematuria	May indicate cauda equina syndrome or infection
Lower extremity neurological deficit	Progressive or severe neurological deficit in one or especially both lower extremities, weak anal sphincter	May indicate severe nerve root injury or cauda equina syndrome

History

Similar to the evaluation of patients with chest and abdominal pain, a systematic approach should be used to identify LBP red flags. With regard to the elements in the history, Winters et al. suggested using the mnemonic OLDCAAR (*O*nset, *L*ocation, *D*uration, *C*ontext, *A*ssociated symptoms, *A*ggravating factors, and *R*elieving factors) [13]. Onset includes how quickly the pain began, its course, and the age at onset. Location of the pain includes what level of the spine and if there is any radiation of pain to the lower chest, abdomen, or extremities that might suggest a visceral origin or nerve root impingement. Pain in the distribution of the sciatic nerve (buttock, posterior thigh, leg, and/or foot) is very suggestive of lumbosacral nerve root compression and has a sensitivity of 0.95 and a specificity of 0.88 that the patient harbors a herniated lumbar disk or another cause of nerve root impingement [14]. Deyo et al. estimate the likelihood of a surgically important lumbar disk in a patient without sciatica as being 1 in 1,000 [14]. Duration of more than 4–6 weeks is worrisome unless the pain is very longstanding. The context in which the pain begins is important. Trauma, a recent history of infection or intervention, and a history of cancer suggest fracture, spinal infection, and spinal metastasis, respectively. Current immunosuppression is associated with infection and tumors. Important associated symptoms include fever, chills, weight loss, and neurological symptoms. Significant aggravating factors which suggest nerve root compression include provocation or aggravation of pain by recumbency and

positive cough, sneeze, and strain effect especially on radicular pain. Relieving factors include improvement with sitting or bending forward at the waist which suggests spinal stenosis and the assumption of certain postures such as a list or reluctance to bear weight on an extremity which can suggest neural compression or musculoskeletal disease. In addition, the patient's past medical history may yield important facts, such as risk factors for aortic dissection or abdominal aortic aneurysm (AAA), previous immunosuppression, previous cancer, and diabetes. Psychosocial history can be important as it relates to intravenous (IV) drug use, cigarette smoking, stress, and a history of other pains in the past.

Physical Examination

The physical examination of patients with acute LBP should be guided by the history of present illness and the past medical history. It should include: vital signs assessment [13], general observation of the patient, a regional back exam, and a thorough neurological screening [14, 18]. Findings suggestive of nonspinal pathology may warrant a careful evaluation of related organ systems (e.g., genitourinary) as many medical and surgical conditions can present with acute back pain.

General Observation

The general appearance of the patient may indicate the presence of serious disease [19]. Are they pale, cachectic, or jaundiced? Do they prefer to stand or lay down? In patients with back pain that does not change with movement, who cannot lie still, and/or appear to be in excruciating pain, the possibility of a ruptured AAA or renal colic should be strongly considered [13]. Are there scars or needle marks that suggest IV drug use and possible vertebral column infection?

Fever in a patient with acute LBP has been considered as an indicator of infection [19, 20]. However, its sensitivity varies considerably from 27% for tuberculous osteomyelitis [21] to 83% for spinal epidural abscess (SEA) [22]. It is important to note that the absence of fever does not rule out an infectious etiology of back pain [13]. Blood pressure measurement is also important. Hypotension in the patient with acute back or abdominal pain should alert the physician to the possibility of a ruptured AAA.

Regional Back Examination

Physical examination of the back should start with a careful inspection of the skin. Localized erythema (epidural abscess, inflammatory disease), hairy patches (spina bifida occulta, meningocele), and birthmarks and café-au-lait spots (neurofibromatosis) should be documented. The presence of bruises on the posterior torso, especially in the older patient, should alert the physician to physical elder abuse [23].

Observe the patient's posture while seated, standing, and walking. Patients with active radiculopathy may prefer to keep their weight on the unaffected limb; they may flex the hip and knee and plantar flex the ankle of the affected limb to reduce tension on an impinged nerve root [24]. Palpate the back, paraspinal muscles, and the spine for bony abnormalities, shift of midline structures, muscle spasm, and tenderness. Vertebral tenderness such as with fist percussion has traditionally been associated with spinal infection, but is nonspecific and can be seen with other causes of LBP including musculoskeletal etiologies [18].

Lumbosacral spine range of motion should be tested by assessing flexion, extension, lateral bending to both sides, and rotation of the spine to both sides while the pelvis remains stationary. Pain with forward flexion is associated with disk disorders, whereas pain with extension is associated with spinal stenosis [25]. Rigidity of the entire spine is observed in ankylosing spondylitis. While any limitation in range of motion should alert the physician to possible underlying spine pathology [26], given the marked variability between patients with and without symptoms, reduced spinal range of motion is of limited diagnostic value [18]. Possible causes of spinal

rigidity include ankylosing spondylitis, infection, severe spondylosis, disk herniation with muscle spasm, and musculoskeletal injury.

Screening Tests for Lumbar Radiculopathy

Straight Leg Raising Test

Lasègue Sign

Straight leg raising or the Lasègue sign is commonly used in a patient with LBP to confirm radiculopathy, usually affecting the L5 and/or S1 nerve roots, as they are involved in about 95% of lumbar disk herniations [14, 27]. The maneuver pulls on the sciatic nerve which in turn stretches the nerve roots which comprise the sciatic nerve (L4, L5, S1–3) [28]. Pain is provoked by compression of the nerve root against a structural abnormality, such as a herniated disk which restricts nerve root movement [28, 29]. Devillé et al. in a systematic review reported a pooled sensitivity for the SLR test of 0.91, but a pooled specificity of 0.26 for surgically documented lumbar disk herniation [30].

In the Lasègue test, the patient lies supine and the examiner places one hand above the knee of the limb being examined. The examiner places his or her other hand under the patient's heel and gradually raises the patient's extended leg, flexing the thigh at the hip (Fig. 2.1). The test is considered positive if pain (sharp or burning) is elicited along the course of the sciatic nerve in the ipsilateral buttock, posterior thigh, posterior leg, and/or foot with elevations of 70° or less. It is important to note that provocation of LBP alone does not indicate a positive SLR test. A positive crossed SLR sign in which pain in the affected lower limb is provoked by raising the contralateral lower extremity is thought to be highly suggestive of nerve root impingement by a herniated or extruded lumbar disk. Devillé et al. found a sensitivity of 0.29, and a specificity of 0.88 for the crossed SLR test [30]. SLR tests are also positive in patients with meningeal irritation (e.g., infection, malignant infiltration) when the finding should be bilateral.

Kernig Sign

The Kernig sign is a variation of the SLR test. While the patient lies supine the thigh is flexed at the hip to 90° with the knee in flexion. The examiner then extends the leg at the level of the knee. The test is considered positive if sciatica is elicited and the patient resists full extension of the knee.

Finally, while performing the Lasègue or Kernig test, dorsiflexing the foot or even the great toe increases the stretching of the tibial and sciatic nerves and can aggravate the pain in the patient with nerve root impingement (see Fig. 2.1). This maneuver is termed Spurling sign [31].

Seated SLR

The seated SLR test is performed by extending the patient's knee while they are seated and assessing for the provocation of symptoms. It has the advantages of reducing the patient's discomfort by not performing SLR with the patient in a supine position and also expediting the physical examination [32].

Several variants of the seated SLR test have been developed. One is to ask the patient, while seated, to extend one knee then the other, or to ask them to perform heel to shin testing. This maneuver mimics the same position of the spine as 90° of SLR when supine, but the degree of stretching of the sciatic nerve is less. It has been suggested that a positive SLR test while seated is equivalent to a supine SLR test that is positive at 65° of elevation [24].

Another variation is the slump test [33], a series of maneuvers designed to increase tension on the lumbosacral nerve roots. Patients start in a seated position with their back straight and they are encouraged to slump, relaxing and flexing the thoracic and lumbar spine, while looking straight ahead. The patient is then asked to flex their neck. The examiner can press on the back of their head to increase neck flexion. The patient is instructed to extend one knee (thus performing a seated SLR maneuver) and then dorsiflex the foot on the same side. The maneuvers are repeated with the other lower extremity. With each movement, the patient is asked to report what they feel. Provocation of

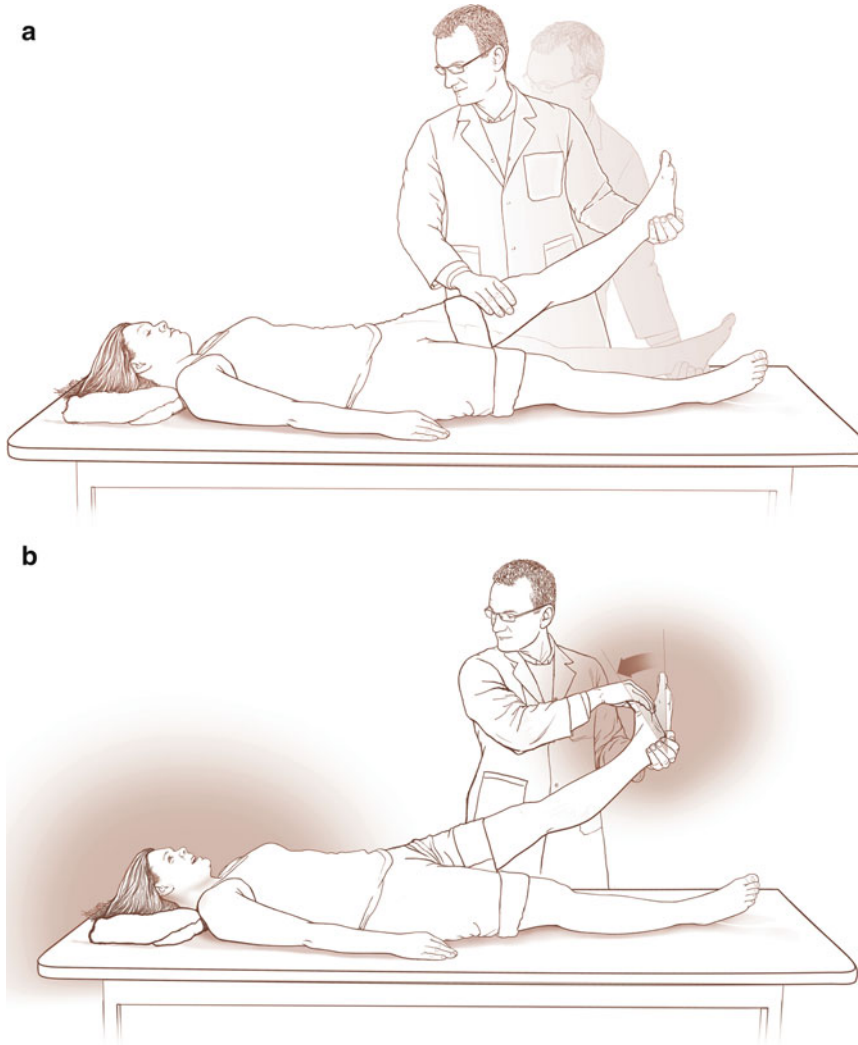

Fig. 2.1 The Lasègue test. The Lasègue sign is tested by passively flexing the hip with the knee extended (**a**). Provocation of ipsilateral radicular lower limb pain is highly suggestive of nerve root impingement. Dorsiflexing the patient's foot while performing a straight leg raising test (**b**) will increase tension on the sciatic nerve and the nerve roots which form the sciatic nerve. Exacerbation of the patient's radicular pain with this maneuver increases the likelihood of lumbosacral nerve root compression. This maneuver is termed Spurling sign. From Bartleson JD and Deen HG, Chap. 4, page 67 and 68. In: Spine Disorders: Medical and Surgical Management by JD Bartleson and HG Deen; Cambridge University Press, 2009. Copyrighted and used with permission of Mayo Foundation for Medical Education and Research

radicular lower limb pain suggests irritation of the sciatic nerve or one of the nerve roots that comprise the sciatic nerve. Subsequent extension of the neck into a neutral position should reduce tension on the lumbosacral nerve roots and lessen the patient's pain and/or enable them to extend the knee farther. In a prospective case–control study of 75 patients with LBP who had undergone MRI for suspected lumbar disk herniation, sensitivity of the slump test was higher (84% versus 52%) than the traditional SLR, but the specificity was lower (83% versus 89%) [34].

Reverse SLR Test

The reverse SLR test is performed with the patient in a prone position. One knee at a time is passively flexed as far as possible trying to touch the

Table 2.2 Symptoms and signs associated with lumbosacral radiculopathy

Root	Typical pain distribution	Dermatomal sensory distribution	Weakness	Affected reflex
L1	Inguinal region	Inguinal region	None	Cremasteric
L2	Inguinal region and anterior thigh	Proximal anterior and medial thigh	Hip flexion Hip adduction Some knee extension	Cremasteric Thigh adductor
L3	Anterior thigh and knee	Anterior and medial thigh	Knee extension Hip flexion Hip adduction	Knee Thigh adductor
L4	Anterior thigh, anteromedial leg	Anterior knee and medial leg	Knee extension Hip flexion Hip adduction	Knee
L5	Posterolateral thigh Lateral leg Medial foot	Anterolateral leg, top of foot, great toe	Foot dorsiflexion, inversion and eversion Knee flexion Hip abduction Toe extension and flexion	Possibly internal hamstring
S1	Posterior thigh and leg, heel, and lateral foot	Posterolateral leg, lateral foot, heel	Foot plantar flexion Toe flexion Knee flexion Hip extension	Ankle Possibly external hamstring
S2	Buttock	Posterior leg and thigh, buttock	Possibly foot plantar flexion Possibly hip extension	Anal reflex Possibly ankle

From Bartleson JD and Deen HG, Chap. 4, page 65. In: Spine Disorders: Medical and Surgical Management by JD Bartleson and HG Deen; Cambridge University Press, 2009. Copyrighted and used with permission of Mayo Foundation for Medical Education and Research.

patient's heel to their buttock. If pain is elicited in the ipsilateral limb, typically in the anterior thigh, it suggests impingement of the L2, L3, or L4 nerve roots which contribute to the femoral nerve and are stretched by this maneuver. Additional extension of the hip after the knee is flexed may increase the sensitivity of this test.

Patrick or FABER Test

The Patrick or FABER (*F*lexion, *AB*duction, and *E*xternal *R*otation) test is used to evaluate for sacroiliac and hip joint pathology. It is performed while the patient is in a supine position. The heel or lateral ankle of the affected lower extremity is placed on top of the contralateral knee and the medial knee on the side of pain is pushed downward causing synchronized flexion, abduction, and external rotation of the ipsilateral hip. If pain is elicited in the groin (typically with slow downward pressure on the knee), this indicates possible hip joint disease. Pain in the sacroiliac area (usually with quick downward pressure on the knee) suggests sacroiliac joint pathology.

Neurological Examination

A careful neurological examination is paramount in patients with LBP. The evaluation should search for evidence of spinal cord compression, nerve root impingement including the cauda equina syndrome, and peripheral nerve dysfunction. The examination should include: (1) assessment of motor function, specifically lower limb strength and coordination; (2) reflexes including deep tendon reflexes, the Babinski sign, and the anal wink reflex; (3) sensation (pain and temperature, touch, vibration, and joint position sense); (4) gait; and (5) rectal tone and strength [13].

All of the lumbosacral spinal nerve roots should be assessed [19]. The signs and symptoms associated with specific lumbosacral nerve root injury are listed in Table 2.2.

Motor Function

Individual muscles can be assessed by testing their strength and tone and gauging their bulk. The L2–L4 nerve roots provide the motor innervation responsible for leg (knee) extension and thigh (hip) flexion and can be tested by having the patient arise from a seated position without the use of their upper limbs or ascend a step. The L5 root is largely responsible for ankle and toe dorsiflexion and foot eversion and inversion and can be tested by heel walk. The S1 nerve root innervates the muscles responsible for foot and toe plantar flexion (in conjunction with the S2 nerve root) and contributes to foot inversion (with the L5 root), and can be tested by toe walking and performing toe lifts while standing on one leg. The intrinsic foot musculature, the bladder, and the external anal sphincter are supplied by the S2–S4 nerve roots.

Reflexes

The knee reflex is supplied by the L2–L4 nerve roots. The ankle reflex is supplied chiefly by the S1 nerve root with some contribution from S2. The internal and external hamstring reflexes are supplied by the L4, L5, S1, and S2 nerve roots. The internal hamstring reflex is said to be supplied more by the L5 and the external hamstring more by the S1 nerve root, but asymmetries in the hamstring reflexes are hard to judge and correlation with a specific nerve root injury is unreliable. Babinski and Chaddock signs indicate upper motor neuron (corticospinal tract) damage typically above the L1 vertebral level (in most adults the spinal cord ends at the level of the L1 vertebral body). The cremasteric reflex is innervated by L1 and L2 and the superficial anal or anal wink reflex (contraction of the external sphincter in response to pricking or stroking the perianal skin) is supplied by S2–S4. The plantar reflex is innervated by L5, S1, and S2 and consists of the normal plantar flexion of the toes resulting from stimulation of the foot as occurs with Babinski and Chaddock sign testing.

Sensation

Sensation is evaluated using light touch, pin prick, change in joint position, and vibration. Hot and cold stimuli can be used as substitutes for pin prick. The L1 nerve root supplies superficial sensation to the inguinal area. The L2 and L3 nerve roots provide sensation to the anterior and medial thigh. The L4 nerve root is responsible for sensation over the anterior knee, and medial surface of the leg and foot (but not the first dorsal webspace). The L5 nerve root delivers sensation from the dorsal aspect of the foot, including the first dorsal webspace. The S1 dermatome covers the posterior and lateral aspect of the foot and leg. The S2–S4 nerve roots supply sensation to the posterior leg, posterior thigh, buttock, and perianal area.

Gait

Observation of casual gait can reveal significant abnormalities. Trendelenburg sign, due to hip abductor weakness (chiefly the gluteus medius muscle), is observed when the patient stands or walks on one leg and the pelvis on the opposite, non-weight-bearing side drops. The gluteus medius muscle receives innervation chiefly from the L5 and S1 nerve roots. Difficulty with heel walking suggests L5 distribution weakness or peroneal neuropathy or, if bilateral, a peripheral neuropathy. Difficulty with toe walking suggests S1 radiculopathy. Bilateral difficulty with toe walking more than heel walking suggests bilateral S1 radiculopathies rather than peripheral neuropathy [35].

Rectal

Rectal examination in the patient with LBP is performed to assess rectal tone, anal sphincter strength, and sensation and can facilitate testing the superficial anal reflex. It should be performed in patients with significant low back and/or lower limb pain, neurological complaints or deficits,

sphincter complaints, and in association with any red flags [19]. Poor or absent rectal tone in the presence of saddle sensory loss strongly indicates neurological disease such as compression of the cauda equina or lower spinal cord (conus medullaris).

Diagnosis

The physician evaluating a patient with acute LBP should consider two questions when ordering a diagnostic test. Can a diagnosis be established? And how will the information obtained influence management? Findings on plain radiographs and advanced imaging (CT scan, MRI) correlate poorly with symptoms [36–38], and their initial use in the absence of red flags has been deemed unnecessary [39]. The American College of Radiology practice guidelines state that imaging the acute LBP patient is not indicated except in the presence of red flag features, which include recent significant trauma, minor trauma in a patient age >50, weight loss, fever, immunosuppression, history of neoplasm, steroid use or osteoporosis, age >70, known IV drug abuse, or a progressive neurological deficit with intractable symptoms [40].

A recent meta-analysis of randomized controlled clinical trials that compared immediate lumbar imaging versus usual clinical care without immediate imaging for LBP reported no significant differences between the two groups in terms of clinical outcomes [41]. The decision to use any medical test should be based on a risk/benefit assessment. Imaging provides benefit in identifying undiagnosed systemic disease and in operative planning for neural compressive lesions requiring intervention. This must be balanced against substantial cost, radiation exposure, labeling subjects as patients with degenerative spine disease (which is inevitably present but almost always asymptomatic), and provoking interventions which may have little basis in evidence. It is well established that when we image, we intervene [42, 43].

Imaging Studies

This section will focus on imaging studies that provide evidence of structural or anatomic abnormalities that can explain the patient's spine pain. The studies include plain X-rays, MRI, plain CT, and CT myelography. Illustrative examples of all three imaging modalities are shown in Figs. 2.1–2.5. Physiologic studies such as electromyography

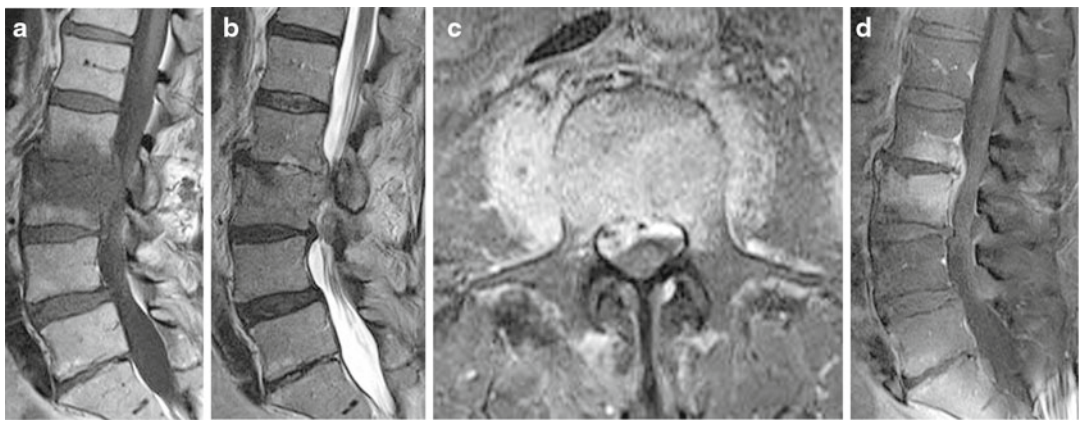

Fig. 2.2 Imaging findings associated with spondylodiscitis. A 65-year-old man with a history of recent abdominal surgery and postoperative sepsis now presents with back pain and right lower limb weakness. Sagittal T1 (**a**)-weighted and T2 (**b**)-weighted MRI images show T1 hypointensity bridging the L2 and L3 vertebral bodies. The central canal is narrowed. Postgadolinium axial (**c**) and sagittal (**d**) images show enhancement in the vertebral bodies, epidural space, and paraspinal tissues consistent with spondylodiscitis. Culture revealed *S. aureus* infection

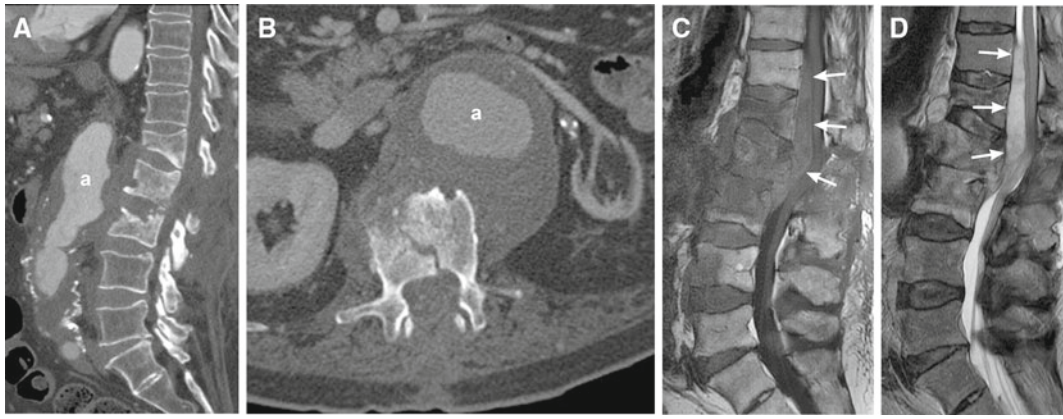

Fig. 2.3 Imaging findings associated with spondylodiscitis. An 85-year-old man presents from another institution with progressive back pain and a history of an aortic graft. A sagittal CT image (**A**) shows multilevel spondylodiscitis with pathologic vertebral fractures in direct continuity with a supragraft aortic pseudoaneurysm (a) which is also seen on the axial image (**B**). Sagittal T1 (**C**)-weighted and T2 (**D**)-weighted MRI images also demonstrate spondylodiscitis of L1–L4 and a large ventral epidural abscess (see *arrows*). Surgical exploration showed Q fever (*Coxiella burnetii*) mycotic aortic aneurysm, epidural abscess, and spondylodiscitis. The patient succumbed to his disease

and nerve conduction velocity testing and radionuclide imaging are typically not performed as part of the emergency evaluation of the patient with back pain.

Plain Radiography

Plain radiography is the imaging technique most commonly available to and used by clinicians to image the lumbar spine. Routine plain lumbosacral spine radiographs are indicated in patients with LBP if the pain has persisted for more than 4 weeks despite conservative management, or if there are red flag risk factors for systemic disease, fracture, infection, or neoplasm. Thoracolumbar spine imaging in the setting of blunt trauma is recommended in patients with a high-force mechanism of injury and any of the following: back and/or posterior midline tenderness, local signs of thoracolumbar injury, abnormal neurological signs, cervical spine fracture, Glasgow Coma Scale (GCS) < 15, a major injury elsewhere in the body which distracts one's attention, and in the setting of alcohol and/or drug intoxication [44].

In a large retrospective study of 3,173 patients, Tamir et al. found that in ambulatory motor vehicle accident trauma patients complaining of upper or LBP, none of the thoracic or lumbar radiographs were positive for fracture or dislocation [45]. If the clinical presentation suggests the presence of potential tumor or infection (history of cancer, weight loss, recent infection, fever, IV drug use, or immunosuppression), plain X-rays should be combined with complete blood count (CBC) and erythrocyte sedimentation rate (ESR), as the sensitivity of X-rays alone for detecting early cancer or infection is not as high as when blood tests are combined with plain films [46, 47].

The standard initial radiographs include two standing views: anteroposterior (AP) and lateral [48, 49]. Radiographs are primarily a low-sensitivity screen for systemic disease. They also enable clinicians to assess lumbar alignment, disk space size, the vertebral bodies, and bone density. Additional views, such as spot lateral views of the L5–S1 disk space, oblique views, and flexion and extension views, should be reserved for patients with musculoskeletal spine problems to assess structure and stability. The AP view of the lumbar spine allows for assessment of the sacroiliac joints. Plain X-rays frequently show abnormalities that are unrelated to the patient's back pain. These include degenerative

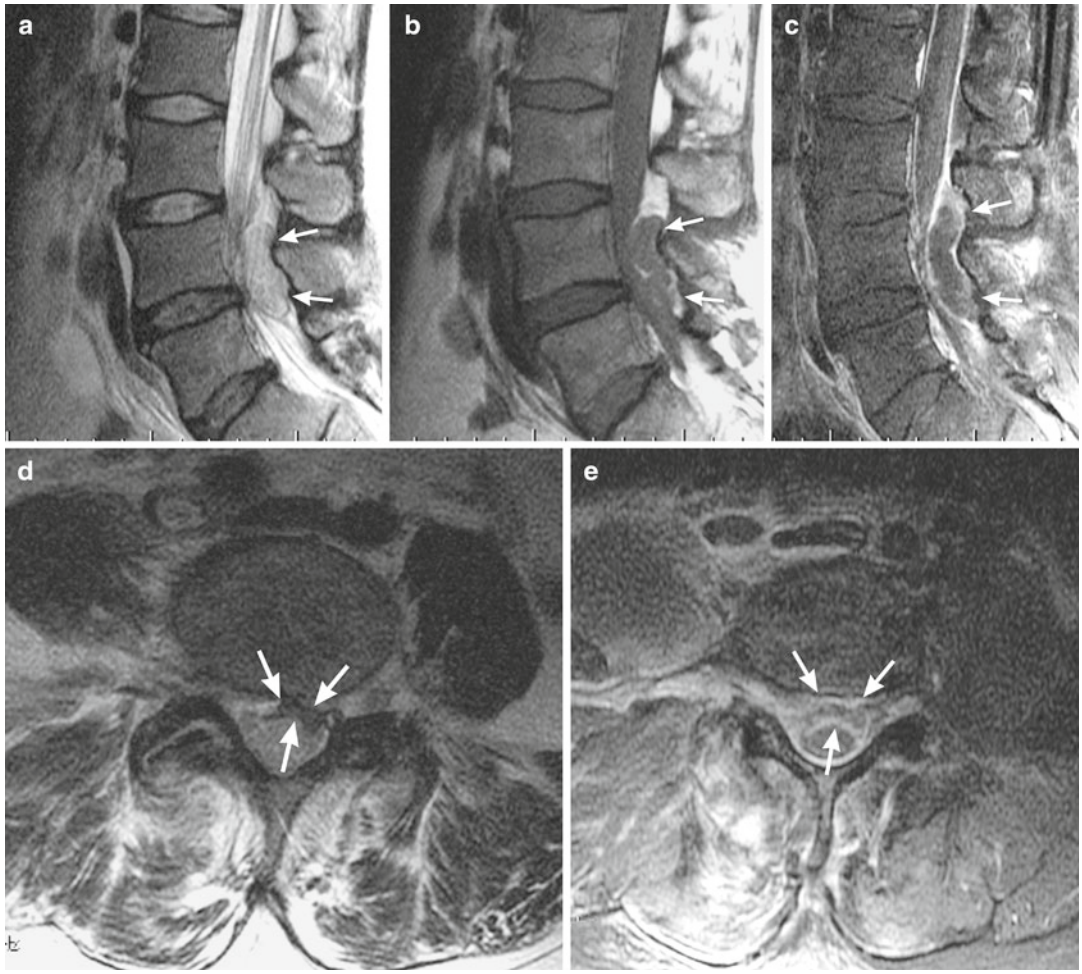

Fig. 2.4 Epidural abscess. A 59-year-old woman presents to the emergency department with a 1-week history of increasing back and right lower limb pain. Her right knee reflex is absent. She has a temperature of 38.6°C. Sagittal T2 (**a**), T1 (**b**), and enhanced T1 (**c**) MRI images show a peripherally enhancing dorsal epidural process compressing the thecal sac (see *arrows*). On axial T2 (**d**)-enhanced and T1-enhanced (**e**) images, the thecal sac is compressed and displaced anteriorly and to the left (see *arrows*) by the posterior mass. Emergent surgical decompression revealed a viridans streptococcal epidural abscess

disk and facet joint disease, spondylolysis, some congenital abnormalities, Schmorl nodes, and mild degrees of scoliosis [47].

Advanced Imaging Studies

The three imaging modalities commonly used to help physicians evaluate for anatomic abnormalities are plain CT, MRI, and CT myelography. The factors which influence the decision regarding which diagnostic test to use in a patient with acute LBP include the tissue of greatest interest, claustrophobia, obesity, presence of internal metallic objects including clips and wires, patient and provider preference, availability, and cost of the test [18].

In this section, we will focus on plain CT and MRI as they are more readily available in all clinical settings (outpatient, inpatient, and emergency department) and most commonly used for the initial evaluation of many patients with back pain.

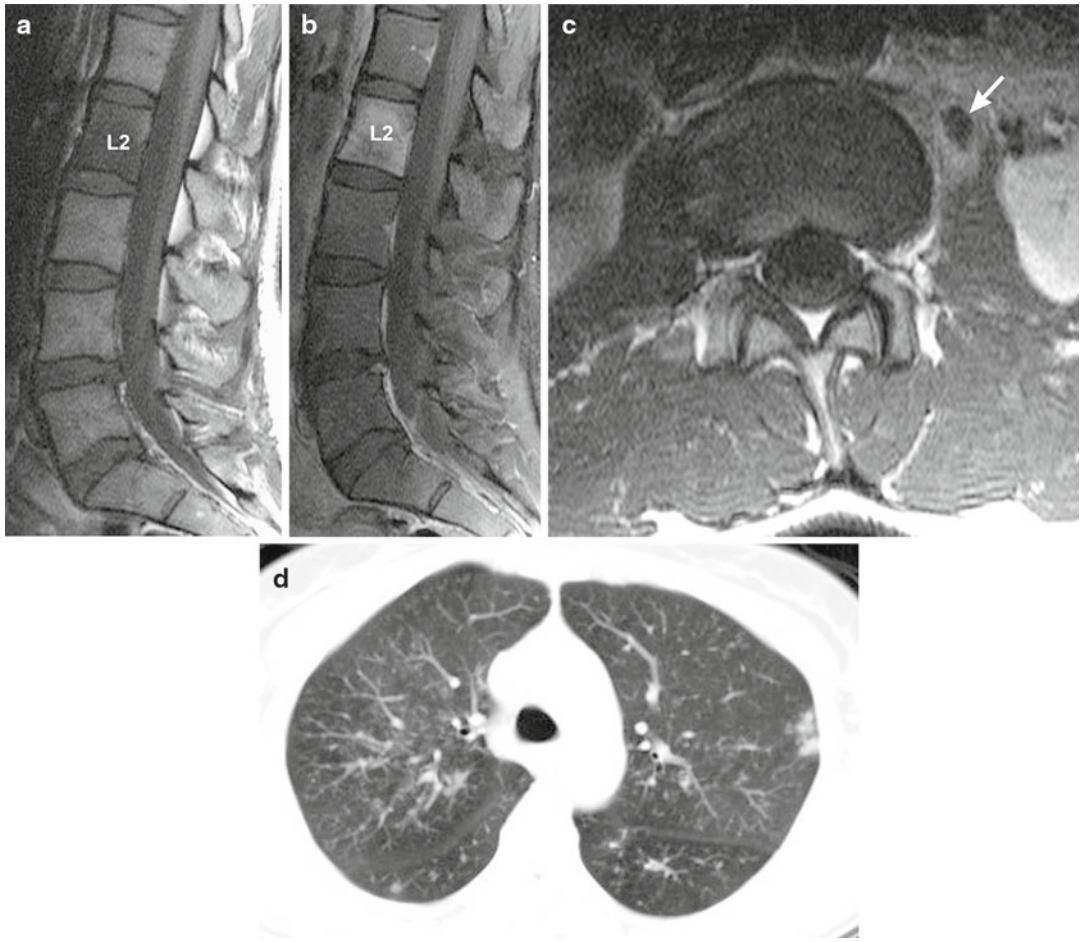

Fig. 2.5 Spinal tuberculosis. A 48-year-old woman presents with upper lumbar and abdominal pain. Pre (**a**)-gadolinium and post (**b**)-gadolinium-enhanced sagittal MRI images show T1 hypointensity and enhancement confined to the L2 vertebral body while the disks are unaffected. On axial T1-enhanced image (**c**), there is a small peripherally enhancing tissue collection in the left psoas muscle adjacent to the L2 vertebral body (see *arrow*). Biopsy revealed *Mycobacterium tuberculosis* (TB). Up to 50% of TB spine infections will spare the disks. Chest CT demonstrated her pulmonary disease (**d**)

Computed Tomography

CT scan utilizes multiple X-ray beams which are projected at different angles to generate axial cross-sectional images of the lumbar spine. Compared to MRI, CT has superior spatial resolution, and enables the clinician to better demonstrate bony pathologies including fractures, bone destruction, and facet joint disease [50, 51]. Also, CT scan can be used as a diagnostic test in patients with contraindications to MRI (e.g., internal metallic objects such as a pacemaker or surgical clips in critical locations). Thornbury et al. compared MRI with either plain CT or CT myelography in 95 patients with acute low back and radicular pain due to probable herniated nucleus pulposus-caused nerve compression. There was no statistically significant difference in the diagnostic accuracy among the three modalities [52]. A more recent study by van Rijn et al. also found no evidence that CT was inferior to MRI in the detection of disk herniation [53]. There are no comparative studies with currently available technology. While spine MRI has

changed little over the past 15 years, multidetector CT has been transformed. The data set for a lumbar examination can be obtained in less than 10 s, and then can be reconstructed in any plane with no loss of spatial resolution. CT thus has superior patient acceptance compared with MRI which requires patients to lie in a closed space for about 30 min, and may be a reasonable choice in the radiculopathy or radicular pain patient with a low clinical likelihood of systemic disease. CT has lower sensitivity than MRI in the detection of spine infection or neoplasm.

CT of the chest and/or abdomen and/or pelvis ("whole body CT") is used in many trauma centers as the initial imaging test for trauma patients. These images can be reformatted and used to clear the thoracolumbar spine of significant bony pathology and some soft tissue conditions. Compared to plain radiography, this use of CT has demonstrated superior sensitivity for detecting thoracolumbar spine injury [54, 55].

Magnetic Resonance Imaging

MRI utilizes a potent magnetic field to align chiefly the hydrogen atoms in the body and uses radio waves to alter their alignment, causing the hydrogen nuclei to produce a rotating magnetic field detectable by the scanner. The energy released when the radio waves are turned off produces a signal, which is used to create a magnetic resonance image. MRI has superior contrast resolution when compared with CT, which allows much better visualization of soft tissues, including the intervertebral disks, ligaments, vertebral marrow, and contents of the spinal canal including individual nerve roots and the spinal cord [47]. In a prospective study of 37 patients with suspected vertebral osteomyelitis, X-rays, MRI, and radionuclide studies were performed and their accuracy was compared. MRI had a higher diagnostic yield than plain X-rays or radionuclide bone scanning (sensitivity 96%, specificity 92%) [56]. MRI is the imaging modality of choice for diagnosing spinal infection such as vertebral osteomyelitis and epidural abscess [47]. MRI can show the extent of infection and help to determine if there is a need for surgical intervention. MRI also has superior sensitivity in the detection and characterization of spine neoplasm, including assessment of the need for emergent surgical intervention [47]. In the patient with a fracture on radiographs, MRI provides the best means of characterizing the fracture in terms of its chronicity, benign versus malignant etiology, and whether the patient may be a candidate for vertebral augmentation (vertebroplasty or kyphoplasty).

Regarding nerve root impingement, MRI has superior soft tissue contrast discrimination when compared to CT or CT myelography. MRI is the preferred diagnostic study for the visualization of intrathecal and extrathecal nerve root impingements, especially when the compressing pathology is also a soft tissue (e.g., herniated nucleus pulposus) [47, 57].

Differential Diagnosis

The differential diagnosis of a patient with LBP is broad (Table 2.3). In this section, we will cover urgent and emergent conditions which can present with acute lower spine pain as the initial or chief complaint, including infection, tumors, diseases of the aorta, spondylotic conditions (discogenic, spinal stenosis, and spondylolisthesis), and trauma.

Vertebral Infection

Vertebral Osteomyelitis

Vertebral osteomyelitis is one of the etiologies of back pain that can cause significant neurological compromise if misdiagnosed or left untreated [58]. It is defined as an infection of the bones of the spine. It can be caused by hematogenous spread from any source in the body; by direct inoculation arising from injection, trauma, or spinal surgery; or by contiguous spread from adjacent soft tissue infection [59, 60]. Discitis is an inflammation of the vertebral disk space, usually associated with infection. The presentation, evaluation, and management of vertebral osteomyelitis and discitis are very similar. In fact, they

Table 2.3 Differential diagnosis of low back pain[a]

Mechanical low back or leg pain (97%)[b]	Nonmechanical spinal conditions (about 1%)[c]	Visceral disease (2%)
Lumbar strain, sprain (70%)[d]	Neoplasia (0.7%)	Disease of pelvic organs
Degenerative processes of disks and facets, usually age-related (10%)	Multiple myeloma	Prostatitis
Herniated disk (4%)	Metastatic carcinoma	Endometriosis
Spinal stenosis (3%)	Lymphoma and leukemia	Chronic pelvic inflammatory disease
Osteoporotic compression fracture (4%)	Spinal cord tumors	Renal disease
Spondylolisthesis (2%)	Retroperitoneal tumors	Nephrolithiasis
Traumatic fracture (<1%)	Primary vertebral tumors	Pyelonephritis
Congenital disease (<1%)	Infection (0.01%)	Perinephric abscess
Severe kyphosis	Osteomyelitis	Aortic aneurysm
Severe scoliosis	Septic discitis	Gastrointestinal disease
Transitional vertebrae	Paraspinous abscess	Pancreatitis
Spondylolysis[e]	Epidural abscess	Cholecystitis
Internal disk disruption or discogenic low back pain[f]	*Shingles*	Penetrating ulcer
Presumed instability[g]	Inflammatory arthritis (often associated with HLA-B27) (0.3%) Ankylosing spondylitis Psoriatic spondylitis Reiter's syndrome Inflammatory bowel disease Scheuermann disease (osteochondrosis) Paget disease of bone	

[a]Figures in *parentheses* indicate the estimated percentages of patients with these conditions among all adult patients with low back pain in primary care. Diagnoses in *italics* are often associated with neurogenic leg pain. Percentages may vary substantially according to demographic characteristics or referral patterns in a practice. For example, spinal stenosis and osteoporosis will be more common among geriatric patients, spinal infection among injection drug users, and so forth.

[b]The term "mechanical" is used here to designate an anatomical or functional abnormality without an underlying malignant, neoplastic, or inflammatory disease. Approximately 2% of cases of mechanical low back or leg pain are accounted for by spondylolysis, internal disk disruption or discogenic low back pain, and presumed instability.

[c]Scheuermann disease and Paget disease of bone probably account for less than 0.01% of nonmechanical spinal conditions.

[d]"Strain" and "sprain" are nonspecific terms with no pathoanatomical confirmation. "Idiopathic low back pain" may be a preferable term.

[e]Spondylolysis is as common among asymptomatic persons as among those with low back pain, so its role in causing low back pain remains ambiguous.

[f]Internal disk disruption is diagnosed by provocative discography (injection of contrast material into a degenerated disk, with assessment of pain at the time of injection). However, discography often causes pain in asymptomatic adults, and the condition of many patients with positive discograms improves spontaneously. Thus, the clinical importance and appropriate management of this condition remain unclear. "Discogenic low back pain" is used more or less synonymously with "internal disk disruption".

[g]Presumed instability is loosely defined as greater than 10° of angulation or 4 mm of vertebral displacement on lateral flexion and extension radiograms. However, the diagnostic criteria, natural history, and surgical indications remain controversial.

typically occur together (spondylodiscitis) and therefore will be discussed together. Vertebral osteomyelitis and disk space infection account for 1% of all skeletal infections [61], and the incidence seems to be increasing probably due to a greater number of older people, a rise in the prevalence of IV drug abuse, and more spinal injections and surgical procedures [62].

In a systematic review of 14 studies with 1,008 patients with vertebral osteomyelitis, Mylona et al. found that back pain was the initial symptom in 86% of patients, followed by fever in 60% of the cases [61]. Neurological symptoms including radiculopathy, limb weakness or paralysis, dysesthesia or sensory loss, and urinary retention were reported in 34% of the cases. Of the studies that reported the vertebral level involved, the lumbar area was affected in 58% of the patients [61]. Usually the pain is well localized, reproducible upon palpation of the spine, and worse at night and with weight-bearing and activity [59, 60]. In a case series of 41 patients with confirmed pyogenic infectious spondylitis, the prevailing clinical symptom was focal back pain aggravated by percussion [63]. Fever may be present [61], although its absence does not exclude the possibility of infection [13]. Other constitutional symptoms such as chills, night sweats, weight loss, and malaise can also occur [64]. Patients should be questioned about possible predisposing factors or events, including underlying illnesses, hospitalization, invasive procedures, injection drug use, and travel [59].

The initial evaluation of patients with suspected vertebral osteomyelitis should include: ESR, C-reactive protein (CRP), blood cultures (positive blood cultures can prevent the need for more invasive procedures such as CT-guided or open biopsy [65]), and plain radiographs of the painful portion of the spine. It is important to note that radiographic findings characteristic of vertebral osteomyelitis, such as narrowing of the disk space [66], are not apparent for up to 4–8 weeks after the onset of infection [56]. If focal spinal tenderness and/or an elevated ESR are present, plain films are negative, and the suspicion of spine infection is high, MRI with gadolinium enhancement is recommended for further evaluation [59, 65]. Findings include T2 hyperintensity in the disk, T1 hypointensity in adjacent vertebral bodies, and enhancement in the vertebral bodies, disk, epidural space, and paraspinal tissues [56]. CT scanning is primarily useful in providing guidance for percutaneous biopsy, which can rapidly achieve a diagnosis [64, 65].

Tuberculous spondylitis (Pott disease) is the most common spine infection worldwide and its incidence is increasing in the USA. On MRI, it may be indistinguishable from pyogenic infection, but in up to 50% of cases will spare the disk, presenting as vertebral lesions with paraspinal or epidural extension [67].

The mainstay of treatment for vertebral osteomyelitis and/or discitis is the prompt administration of antibiotics to reduce the incidence of subsequent adverse outcomes including neurological compromise, vertebral destruction, and abscess formation.

Epidural Abscess

SEA is a suppurative infection of the epidural space, usually arising from hematogenous dissemination, direct inoculation of the spinal canal, or contiguous spread. It is a rare disorder, comprising 0.2–2 cases per 10,000 hospital admissions [68], although its incidence seems to have increased likely due to aging of the population, more spinal injections and surgical interventions, and increased IV drug abuse. A population-based study in Minnesota, from 1990 to 2000, found the incidence of spontaneous epidural abscess to be 0.88 case per 100,000 person-years (95% CI 0.27–1.48) [69]. Risk factors include procedures (e.g., epidural catheter placement [70] and paraspinal, peridural, or spinal injections [71]), diabetes mellitus, alcoholism, HIV infection, trauma, tattooing, acupuncture, contiguous bony or soft tissue infection, bacteremia secondary to distant infection, and IV drug abuse [72, 73].

The presenting symptom is usually severe midline back pain (70%), followed by fever (66%) [13, 68]. In a retrospective study of 31 cases of SEA due to *Staphylococcus aureus*, the lumbar or lumbosacral region was the most frequently involved site (61.3%) [74].

The characteristic triad (fever, back pain, and neurological deficits) was initially present in just 13% of patients with SEA [75]; the absence of any one of the symptoms should not preclude consideration of SEA [13]. Progression of symptoms has been reported to occur in four stages (1) back pain at the affected spinal level; (2) radiculopathic pain radiating from the involved spinal area; (3) decreased motor strength, sensory deficits, and bowel and bladder dysfunction; and (4) paralysis [72, 73].

Early recognition and treatment is critical to avoid permanent disability. Once strongly suspected, the initial diagnostic evaluation should include: CBC, ESR, and CRP. As previously discussed, MRI with gadolinium enhancement is the imaging modality of choice for diagnosing spinal infection such as vertebral osteomyelitis and epidural abscess [47]. MRI is less invasive, can show the full extent of infection (longitudinal and paraspinal), and help to determine if there is a need for surgical intervention. Antibiotic treatment alone or following CT-guided needle aspiration can be utilized in selected cases [72]. Surgery is the treatment of choice for most patients and consists of decompressive laminectomy, drainage, and debridement and culture of infected tissues. Surgery is reserved for willing patients with acceptable operative risk, paralysis present for no longer than 24–36 h, and no evidence of panspinal infection [73]. Empiric intravenous antibiotic therapy should be started with vancomycin and a third- or fourth-generation cephalosporin until culture results are available. Staphylococcal, streptococcal, and gram-negative bacteria should be covered [72] (Figs. 2.2–2.5).

Tumors

Benign and malignant nonneurogenic tumors of the spine as well as primary neurogenic tumors of the spine can present with LBP (Table 2.4). While malignant primary and metastatic neoplasms account for less than 1% of the episodes of LBP in primary care practice, they are the most common systemic disease affecting the spine [14, 46]. The spine is one of the most common sites of metastasis, with the most frequent primary tumors being breast (17%), lung (16%), prostate (9%), and kidney (7%) [76].

Table 2.4 Tumor types

Benign nonneurogenic tumors of spine
Osteoid osteoma
Osteoblastoma
Osteochondroma
Chondroma
Aneurysmal bone cyst
Hemangioma
Giant cell tumor
Eosinophilic granuloma
Malignant nonneurogenic tumors of spine
Chordoma
Chondrosarcoma
Osteosarcoma
Ewing sarcoma
Multiple myeloma
Lymphoma
Metastatic tumors
Extradural
Often in bones of spine
Meningeal
Carcinomatosis and lymphomatosis
Intradural/intramedullary
Metastases within the spinal cord
Neurogenic tumors
Intradural/extramedullary
Nerve sheath tumors (schwannoma, neurofibroma)—can be extradural
Meningioma
Lipoma of filum terminale
Paraganglioma—can be extradural and extraspinal
Intradural/intramedullary
Astrocytoma
Ependymoma
Hemangioblastoma
Extradural tumor-like conditions
Extramedullary hematopoiesis
Epidural lipomatosis
Sarcoidosis
Paget disease of bone
Vertebral hemangioma
Synovial cyst
Intradural tumor-like conditions
Dural and spinal cord vascular malformations
Syringomyelia not associated with intramedullary tumor
Sarcoidosis
Arachnoid cyst—can be extradural

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In a retrospective study of 337 patients with a radiographically verified diagnosis of spinal epidural metastases (SEM), one out of every five patients presented with SEM as the initial manifestation of malignancy [77].

Malignant tumors can metastasize to the vertebrae and cause pain without neurological symptoms. Back pain is the presenting symptom in 90% of patients with tumors of the spine [78], and is usually constant, progressive, and not relieved by rest. Often, it is worse at night, waking the patient from sleep. It is focal to the level of the lesion and may be associated with lower extremity weakness, or symptoms of radiculopathy [60].

If malignancy is suspected, useful laboratory studies include ESR, CRP, CBC, and serum calcium level. Elevated ESR and CRP strongly correlate with systemic neoplasia [46, 60, 79]. It is important to note that ESR and CRP are acute phase reactants and can be elevated in the setting of inflammation or infection as well as cancer. Additionally, blood test results can be normal in the presence of metastatic malignancy. In the setting of suspected tumor, ancillary studies can include plain radiography, MRI, CT, and radionuclide imaging. Plain radiographs are less sensitive than other imaging techniques. MRI is more sensitive and specific than other imaging tests for detecting tumors which cause back pain [47, 57]. The management of patients with back pain secondary to benign and malignant tumors will depend on the presence of neurological symptoms, spine stability, and tumor type [13]. Findings of spinal cord or cauda equina compression should prompt consideration of emergent surgical intervention. For patients without neural compression or with compression and a stable course, consultations with an oncologist, radio-oncologist, interventional radiologist, and spine surgeon are recommended.

Signs and symptoms of spinal cord or cauda equina compression by benign or malignant tumors mandate urgent or emergent assessment and treatment. Because of its importance, the following section focuses on spinal cord and cauda equina compression.

Spinal Cord and Cauda Equina Compression

Extrinsic spinal cord and cauda equina compression result in epidural spinal compression syndromes (ESCS). While rare, spinal cord, cauda equina, and conus medullaris compression need to be considered by the clinician evaluating a patient with acute and chronic LBP. Up to 90% of cases are due to SEM, but other etiologies include SEA, massive disk herniation, and spinal epidural hematoma. Intradural tumors can also present with back pain and spinal cord or cauda equina compression. In a review of 337 patients with SEM at Mayo Clinic, the thoracic spinal level was involved in 61%, the lumbosacral level in 29%, and the cervical level in 10% [80]. The conus medullaris forms the distal, bulbous part of the spinal cord. The spinal cord typically terminates at the lower end of the L1 vertebral body in adults, but can end anywhere from the twelfth thoracic vertebra to the interspace between the second and third lumbar vertebrae. The cauda equina consists of a sheaf of bundled lumbosacral nerve roots which run from the bottom of the spinal cord to the end of the vertebral (spinal) canal within the sacrum. It can be clinically difficult to differentiate cauda equina syndrome from conus medullaris compression (Table 2.5).

The first symptom of ESCS due to SEM is usually back pain [81, 82] which precedes neurological symptoms by an average of 7 weeks [83]. Pain gradually increases and may be accompanied by a radicular component which is more common with lumbosacral level involvement [82]. Motor weakness is one of the most common symptoms, affecting 60–85% of patients [82, 83]. If the spinal cord is compressed, the weakness typically follows a corticospinal tract pattern, preferentially involving the flexors in the lower extremities, and if above the thoracic spine, the extensors of the upper limbs [83]. Below the level of spinal cord compression, hyperreflexia and extensor plantar responses are typically present [83]. Delayed recognition of ESCS due to SEM reduces the likelihood of a good outcome after treatment [83, 84].

Table 2.5 Conus medullaris versus cauda equina syndrome

	Conus medullaris	Cauda equina
Vertebral level of injury	Depends on level of termination of spinal cord, usually vertebral level T12–L1; injury is usually to sacral spinal cord (S1–S5)	Between L1 or L2 and the sacrum with injury to multiple lumbosacral nerve roots
Causes	Fracture, primary and secondary tumors, vascular injury, infection, spondylosis (usually disk)	Fractures, primary and secondary tumors, infection, spondylosis (disk or spondylolisthesis), ankylosing spondylitis (rarely)
Pain	Less common and less severe; usually bilateral and affecting perineum and/or thighs	Often and more severe, can be symmetric or asymmetric and typically radicular (sciatica)
Motor findings	Less severe, more symmetric, fasciculations more likely, usually restricted to sacral roots	Less symmetric, can be more severe, fasciculations less common
Reflex loss	Ankle reflex only	Ankle and knee reflexes may be absent
Sensory findings	Bilateral perineal, more likely symmetric, loss of pain and temperature with possible retention of touch	Less symmetric, perineal and lower limb may be affected, all types of sensation can be affected
Bowel and bladder function	Usually early and prominent for both urinary and rectal sphincters	Occurs later and is less severe for both bowel and bladder
Sexual function	Erection and ejaculation more likely to be affected	Less likely to be affected
Onset (depends on cause)	More likely to be acute	More likely to be gradual
EMG findings	Restricted to sacral myotomes, usually bilateral	Multiple lumbosacral levels, usually bilateral root involvement
Prognosis (depends on etiology)	Relatively worse	Relatively better

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In the lumbar spine ESCS affects the lumbosacral nerve roots that comprise the cauda equina and typically produces a cauda equina syndrome. Presenting symptoms include LBP, radicular lower limb pain on one or both sides, motor and/or sensory deficits, and sphincter problems [85]. Common neurological examination findings include: positive SLR or other signs of nerve root irritation (unilateral or bilateral), decreased deep tendon reflexes in the lower limbs, and motor and sensory deficits in the distribution of one or more lumbosacral nerve roots. Urinary retention (and resulting overflow incontinence) is the most consistent finding [86–88]. Any history suggestive of urinary retention should prompt a check of postvoid residual volume. The most frequent sensory loss affects the perineal region, buttocks, and posterior thighs and legs [86–88]. Anal sphincter tone is decreased in up to 80% of patients [86–88].

Expedited imaging is crucial in the evaluation and management of patients with ESCS [75, 81, 89]. All patients with suspected spinal cord or cauda equina compression should undergo urgent MRI, and if MRI is not available or the patient cannot undergo MRI, plain CT or CT myelography should be obtained [57]. Recognition of spinal cord or cauda equina compression by cancer should prompt consideration of systemic corticosteroid administration and evaluation by a spine surgeon. Two corticosteroid regimens can be used: a high-dose regimen for patients with paraplegia or rapidly progressing symptoms and a lower-dose regimen for patients with pain but minimal neurological dysfunction [84]. The high dose of corticosteroid (usually dexamethasone)

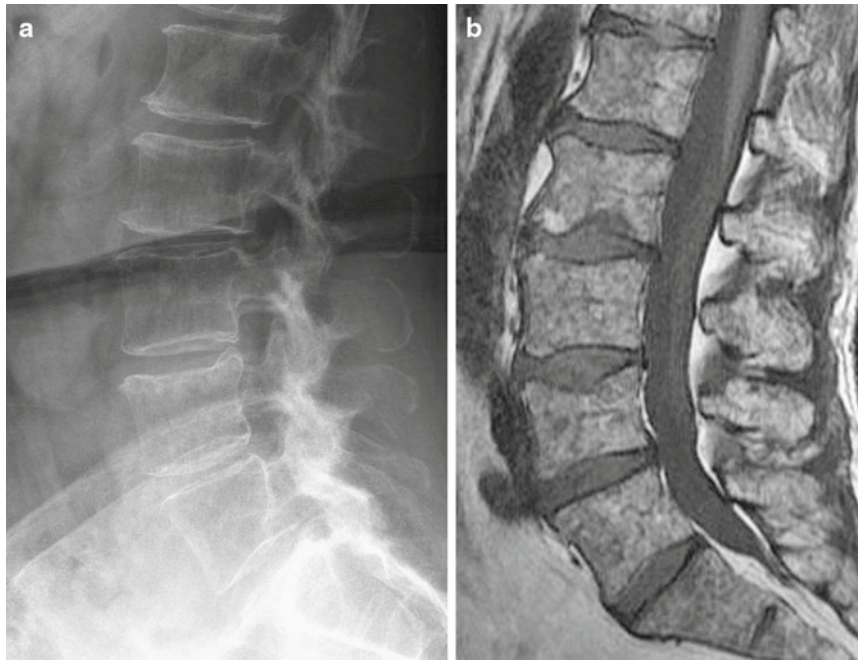

Fig. 2.6 Imaging findings of multiple myeloma affecting the spine. A 70-year-old man presents with low back pain. A lateral radiograph (**a**) shows heterogeneous loss of bone density throughout the lumbar spine. The possibility of multiple myeloma was raised and confirmed on subsequent sagittal T1-weighted MRI (**b**), which demonstrates innumerable tiny marrow-replacing lesions

has more evidence of benefit and a relatively high rate of serious side effects while the low dose has fewer side effects but less data to support its use [84]. Patients with small epidural lesions and normal neurological examinations do not need corticosteroids [84].

Patients with ESCS require a specific diagnosis (tumor and what type, disk, infectious agent, or hematoma). If the patient has a history of a specific tumor with a predilection for spinal metastasis, it can be assumed that the same cancer is responsible for a new SEM. For unknown mass lesions, diagnosis is established by imaging-guided needle biopsy or culture or at the time of surgical intervention to remove tumor or drain pus. The definitive treatment of patients with ESCS is usually surgical decompression, but can vary depending on the type of tumor and whether or not an SEA needs surgical intervention. Patients with progressive or severe cauda equina or spinal cord compression due to a large herniated disk will typically require emergent or very urgent laminectomy and discectomy, preferably within 24–48 h of onset [85, 90]. Patients with SEA will require antibiotics and usually will require surgical drainage. The treatment of patients with SEM can be radiotherapy alone or radiotherapy and surgery depending on their initial presentation and the type of tumor [91]. Rarely, patients with SEM might be treated with surgery alone (e.g., a patient with a single metastasis and gross total surgical resection) or chemotherapy alone (e.g., lymphoma). Surgery is more likely to be recommended if there is spinal instability or the tumor is not radiosensitive (Figs. 2.6–2.8).

Vascular Disorders: Thoracic Aortic Dissection and Abdominal Aortic Aneurysms

Thoracic Aortic Dissection

One of the causes of back pain that presents a diagnostic challenge for physicians is thoracic aortic dissection (TAD) [92]. A recent review of acute aortic dissection found a reported incidence

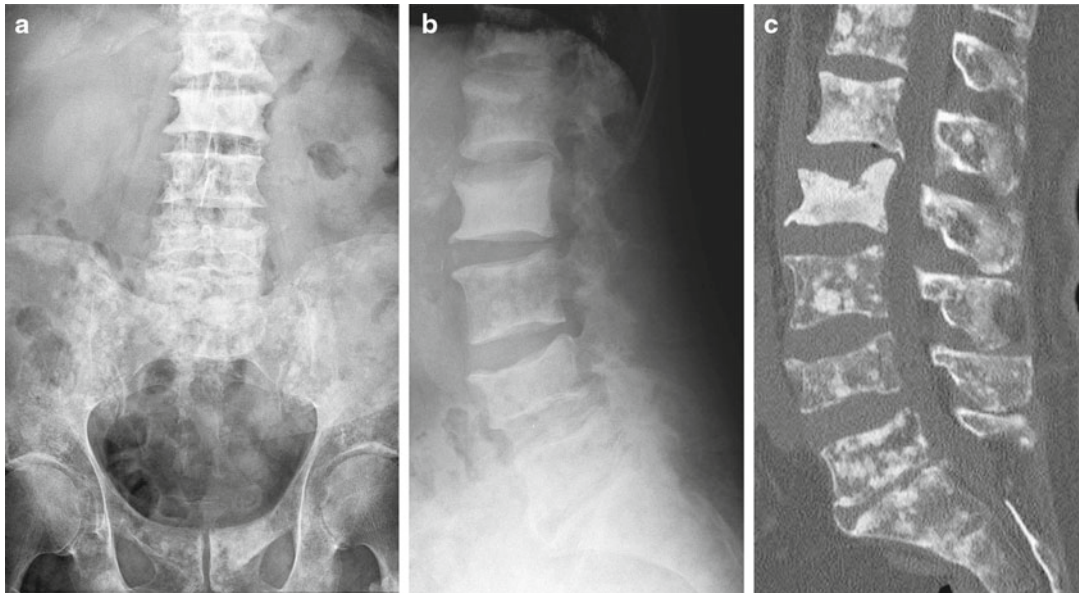

Fig. 2.7 Metastatic prostate cancer affecting the lumbar spine. Frontal (**a**) and lateral (**b**) radiographs in a man with low back pain reveal extensive blastic (bone-forming) metastases due to prostate cancer. The discrete lesions are better seen on a sagittal CT image (**c**)

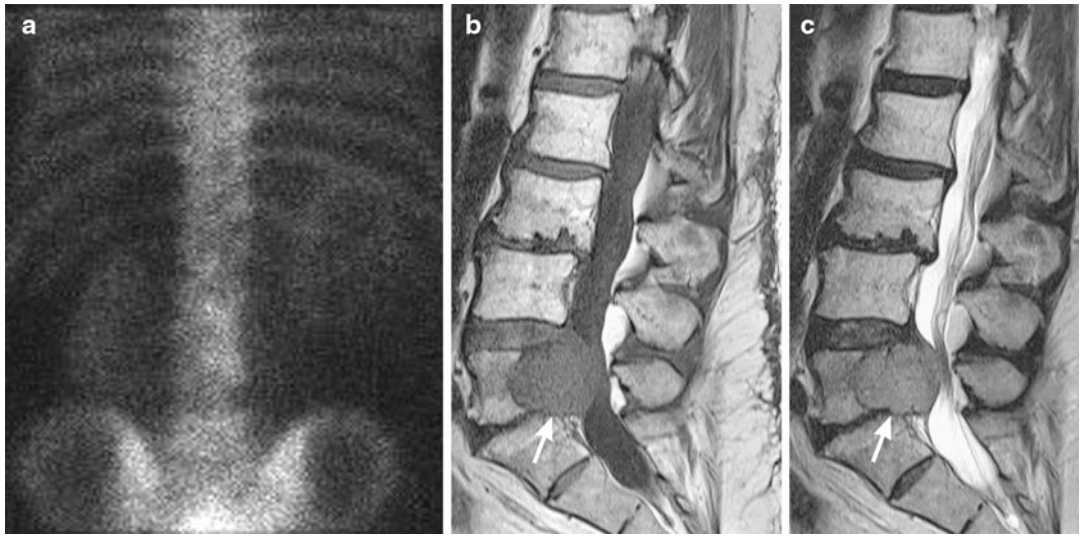

Fig. 2.8 Epidural metastatic tumor compressing the cauda equina. A patient with known colon cancer presents with a cauda equina syndrome despite a recent tumor surveillance radionuclide bone scan (**a**) which fails to show any discrete lesions. Subsequent sagittal T1 (**b**)-weighted and T2 (**c**)-weighted images show a large metastatic lesion occupying the posterior aspect of L5 and extending into the epidural space, effacing the thecal sac (see *arrows*)

of 3.5 cases per 100,000 people per year; 20% of patients died before reaching hospital and another 30% during hospital admission [93]. TADs can be divided into those affecting the ascending aorta (Stanford type A and DeBakey types I and II) and those affecting the aorta more distally (Stanford type B and DeBakey type III). Left untreated, 75% of patients with dissection of the ascending

aorta die within 2 weeks [94]. TAD is more frequent in men between the ages of 50 and 70 years, and the most important predisposing factor is systemic hypertension [95]. Other risk factors include preexisting aortic aneurysm, atherosclerosis, connective tissue disorders (e.g., Marfan syndrome, Ehlers-Danlos syndrome), bicuspid aortic valve, and vascular inflammation (e.g., Takayasu arteritis, giant cell arteritis) [93–95].

The traditional presentation of chest pain that starts suddenly and is described as ripping or tearing in a patient with hypertension is no longer the rule [95–98]. While 85–95% of patients with TAD report pain which is usually abrupt in onset and severe, only half describe a ripping or tearing quality [93, 95, 97]. The pain can affect the front or back of the chest, the back, or the abdomen [95]. The location of the pain can move, depending on the site of tear and its direction of extension (neck, back, or abdomen). Dissections of the descending aorta are more likely to cause back and abdominal pain than chest pain [97]. Painless presentations are reported in 10% of patients [93, 95], especially those with neurological findings such as cerebral, peripheral nerve, or spinal cord ischemia [99, 100]. 10–20% present with syncope, often accompanied by other symptoms [95, 98].

Physical examination findings in a patient with acute TAD include: (1) difference in pulse amplitude between arms, (2) aortic diastolic murmur, and (3) blood pressure differential between arms. A prospective study of 250 patients with clinical suspicion of acute aortic dissection (128 patients with a confirmed diagnosis) found that a difference in systolic blood pressure of more than 20 mm Hg between the arms was a significant independent predictor of TAD [101]. A significant pulse amplitude difference and a systolic blood pressure difference of >20 mm Hg between arms should raise suspicion for TAD, but these findings do not establish the diagnosis. A systematic review by Clark et al. found that the pooled prevalence for inter-arm blood pressure differences in healthy subjects was 20% for a difference of ≥10 mm Hg [102]. The prevalence of asymmetry was greater in patients with high blood pressure and cardiovascular disease [102].

Emergent diagnostic imaging with CT, transesophageal echocardiogram (TEE), or MRI should follow suspicion of TAD. Multidetector CT is the initial modality of choice because it provides precise information about the intraluminal and extraluminal structures of the entire aorta and main aortic branches [103]. The diagnostic accuracy of CT for aortic dissection is nearly 100% [104–106]. TEE is a useful bedside technique to evaluate patients with suspected acute TAD who are hemodynamically unstable. Pooled sensitivity and specificity with TEE for TAD have been reported as 98% and 95%, respectively [107]. The main disadvantages to TEE are operator dependence [108] and inability to visualize the distal part of the ascending aorta [109]. A recent systematic review of TEE, CT, and MRI for the diagnosis of TAD found that all three techniques provided equally reliable results [107]. MRI is seldom used in the emergent setting as the initial imaging technique due to lack of availability, time delays to obtain images, and restricted patient access and monitoring during the study.

When recognized, the patient with suspected TAD should be immediately transferred to the closest emergency department [13] and admitted to an intensive care unit. The treatment will be either medical or surgical depending on the localization of the tear [110].

Abdominal Aortic Aneurysm

AAAs are much more common than thoracic [111]. In 2000, AAA was the 16th leading cause of death in the USA with nearly 16,000 fatalities [112]. This is likely to be an underestimate because many sudden or unattended deaths are not correctly attributed to AAA. Risk rupture increases with aneurysm size [111]. Although most AAAs never rupture, the mortality rate is 80% when rupture does occur [113]. The condition is more common in the elderly [13]. It is estimated that the prevalence of AAA in patients over age 65 years ranges between 4% and 8% and increases with every decade [114]. Risk factors include smoking [115, 116], hyperlipidemia, coronary artery disease, diabetes, connective tissue disorders, and a family history of AAA [13, 114–116].

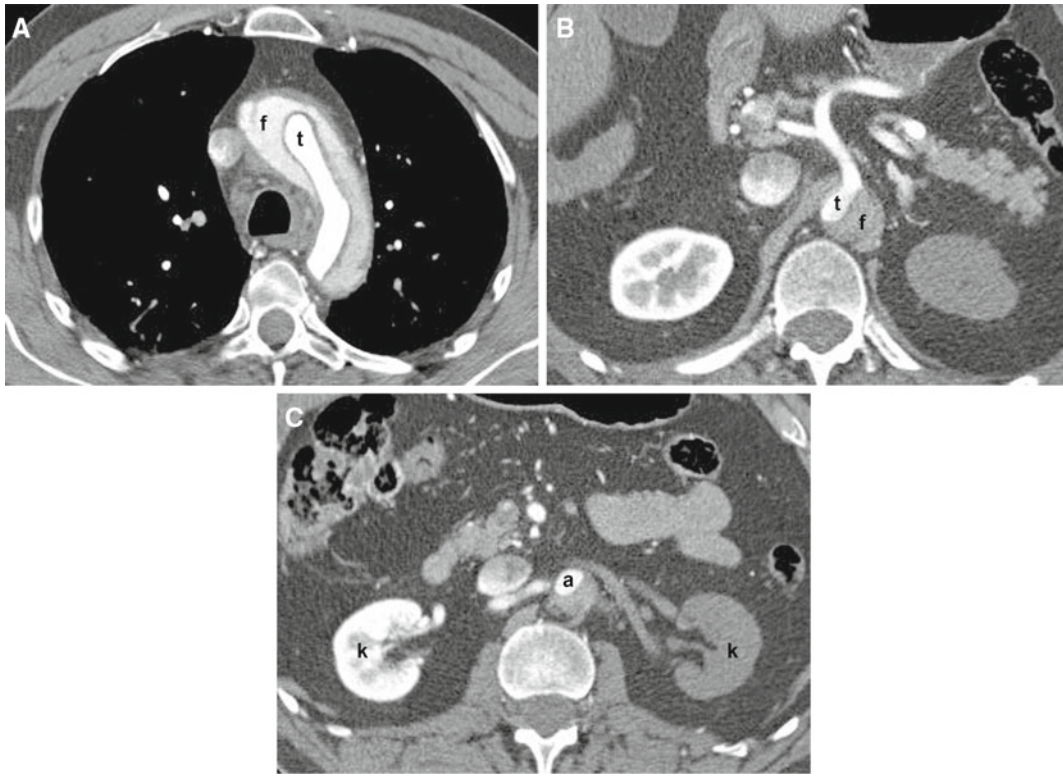

Fig. 2.9 Images of a TAD. A 60-year-old man presents to the emergency department with the acute onset of severe thoracolumbar back pain. A CT scan showed Stanford type A and DeBakey type I thoracic aortic dissection which extended from the aortic valve to the aortic bifurcation. A CT image (**A**) at the aortic arch shows differential opacification of the true (t) and false (f) lumina. A CT image at the level of the celiac plexus (**B**) shows a small true lumen (t) filling the celiac plexus, while the false lumen (f) does not opacify. A lower CT image (**C**) shows an opacified small true aortic lumen (a). The right renal artery opacifies, and the right kidney (k) enhances, while the left kidney (k) is ischemic

The clinical presentation of AAA is extremely variable, ranging from no symptoms to flank pain resembling renal colic to retro- or intraperitoneal rupture and shock. Similar to TAD, the classic clinical presentation for rupturing AAA (the triad of hypotension, abdominal pain, and pulsatile mass) is not the most common, occurring in less than half of patients [117]. Back pain, left lower quadrant abdominal pain, flank pain, syncope, or lower extremity paresthesia can be presenting symptoms. Reports of peripheral nerve injury with weakness of hip flexion and knee extension due to femoral neuropathy have been associated with ruptured AAA [118].

Once the diagnosis of symptomatic AAA is suspected, prompt diagnostic imaging should follow. Ultrasound is the preferred modality to screen, assess, and follow abdominal aneurysms because it is accurate (sensitivity and specificity, 99%), inexpensive, and noninvasive [111, 119, 120]. CT is the preferred imaging technique to delineate the shape and extent of the aneurysm and its relationship with the visceral and renal vasculature [111]. CT angiography can provide more detailed evaluation of the AAA and the renal, mesenteric, and iliac arteries [111]. Disadvantages to CT include radiation exposure, IV contrast administration, and higher cost. Magnetic resonance angiography can also be used [111].

The management of patients with asymptomatic AAA will be medical treatment (e.g., beta-blockers), observation, and elective surgical repair [121]. In patients with ruptured AAA, emergent surgical intervention is needed to prevent death (Figs. 2.9 and 2.10).

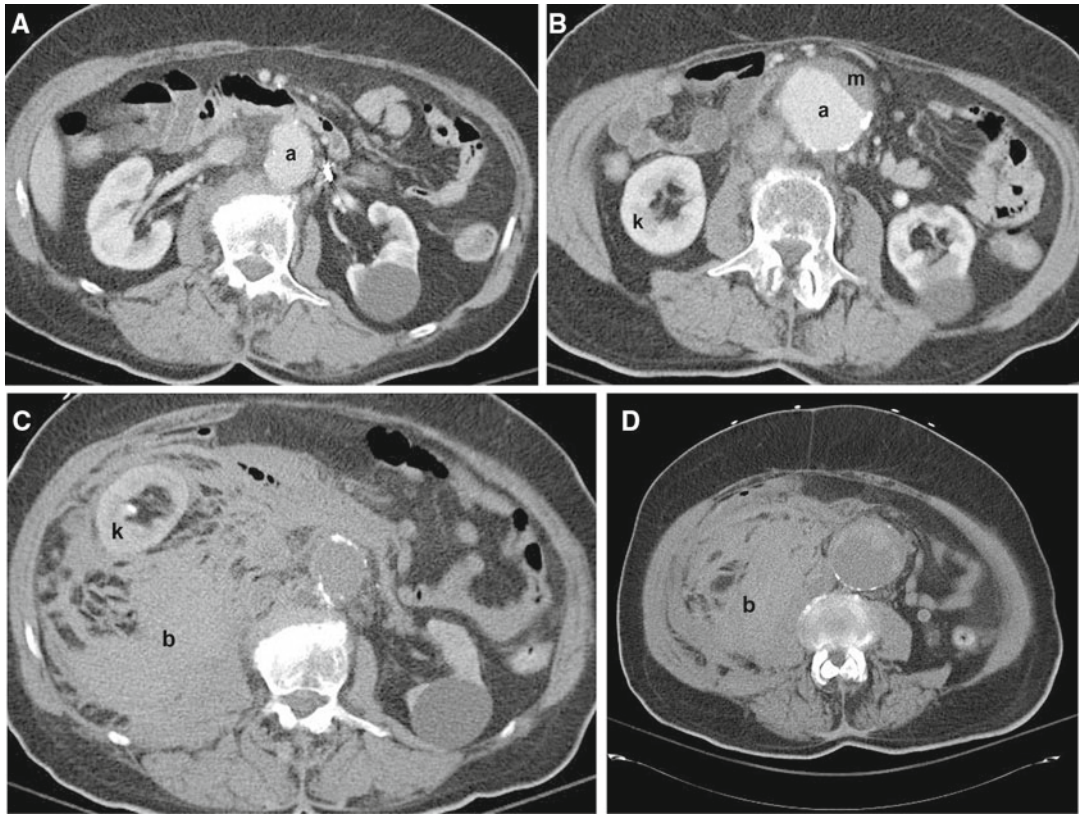

Fig. 2.10 A rupturing AAA. An 80-year-old man presents to the emergency department with new low back and hip pain. He has a known abdominal aortic aneurysm with future plans for an elective repair. He is anticoagulated for atrial fibrillation. CT images (**A**) and (**B**) with IV contrast show a large abdominal aortic aneurysm (a) containing mural thrombus (m) without evidence of hemorrhage. Five hours later while still in the emergency department, he developed cardiovascular collapse, and an emergent noncontrast CT was obtained. CT images (**C**) and (**D**) at the same anatomic levels as the previous images show interval massive retroperitoneal bleeding (b) due to aneurysm rupture. Note the shift of his right kidney (k) anteriorly as a result of the large hemorrhage. He survived surgical repair

Spondylotic Low Back Pain Emergencies

Spondylosis is a general term for usually age-related, wear-and-tear changes affecting the intervertebral disks and vertebrae. Degenerative changes in the facet joints are typically included as are changes in the associated spinal ligaments. Paraspinal muscles may be secondarily affected. Spinal spondylosis is nearly universal with age but is frequently asymptomatic.

Musculoskeletal and mechanical conditions are estimated to account for 97% of adult patients with LBP in primary care (see Table 2.3). Lumbar spondylosis can present with LBP, compression of one or more lumbosacral roots, or an acute cauda equina syndrome which requires urgent or emergent attention. The spinal cord ends in most adults at the level of the body of L1 but can end as high as T12 or as low as the L2 intervertebral disk. Thoracic disk herniations can occur at T11–12 (most common) or T12–L1 and cause LBP. A herniated lower thoracic disk can present acutely with signs and symptoms of compression of the lower spinal cord and requires urgent or emergent evaluation and treatment. Conus medullaris syndrome and CES can present with very

similar manifestations (see Table 2.5). Spondylotic acute CES is significantly more common than an acute conus medullaris syndrome, and CES occurs at the lumbar rather than thoracic level. This section will focus on spondylotic lumbar emergencies.

A large lumbar disk protrusion or extrusion is the most common cause of CES. Other causes include trauma, tumors, infections, spondylolisthesis, lumbar spinal stenosis, synovial cysts, epidural hematomas, postoperative complications, and arachnoiditis. Lumbar spinal stenosis and synovial cysts, while spondylotic in nature, do not usually present acutely. Authors have estimated that about 2% of all patients with discogenic LBP undergo surgery and that disk herniation causing CES accounts for 1–2% of lumbar disk operations [14, 47, 122]. Therefore, the prevalence of discogenic CES among all patients with LBP is about 0.0004 (1 in 2,500 patients) [14, 47].

In one large review, CES was caused by L4–5 herniation in 46% of cases, L5–S1 herniation in 36.9% of cases, and L2 and L3 herniations in 17.1% of cases [122]. Patients may be predisposed to CES if they have a congenitally narrow lumbosacral canal or have acquired lumbar spinal stenosis resulting from a combination of degenerative changes affecting the vertebrae (e.g., spondylolisthesis, spurring), intervertebral disks, facet joints, and ligaments. Many, but not all, patients with spondylotic CES have a past history of LBP and/or lumbosacral radicular pain. Presenting clinical symptoms can include LBP, bilateral or unilateral sciatica, perineal/perianal/saddle sensory loss, lower limb motor weakness, lumbosacral root sensory deficits, difficulty with bladder more often than bowel sensation and control, and sexual dysfunction. Neurological findings include weakness and sensory loss in the distribution of multiple lumbosacral nerve roots on one or both sides, positive straight leg raising signs, reduced perianal and perineal sensation, reduced anal sphincter tone and strength, and absent superficial anal and bulbocavernosus reflexes.

Three different presentations have been reported [88, 123]. The first is suddenly over a matter of hours in a patient without previous symptoms referable to the lumbar spine. The second is a subacute onset after a long history of chronic or recurrent LBP and/or sciatica. The third is slowly and insidiously progressive with eventual sphincter involvement [88, 123]. A subacute onset is typical of discogenic CES, but there can be a tendency to "snowball" at the end with rapid progression of neurological impairment.

Not all patients have all clinical features at onset [124]. In one review, only 19% of patients presented with a characteristic combination of bilateral sciatica, lower limb weakness, saddle sensory loss, and sphincter disturbance [124]. Providers and patients and their families should be aware of the worrisome symptoms and signs that can indicate the development of this serious neurological emergency. Men are somewhat more likely than women to develop an acute CES, and the most common age of onset is between 30 and 60 years old.

CES due to compression by a large lumbar disk is a spine emergency because recovery of strength and sensation and especially bladder, bowel, and sexual function are thought to be dependent upon prompt decompression of the nerve roots within the cauda equina [90].

While everyone agrees that decompressive laminectomy and discectomy are indicated for patients with spondylotic CES, and that sooner is better than later, the exact urgency of surgical intervention is somewhat controversial. Ahn et al. in a meta-analysis reported that there was significant advantage to treating patients within 48 h versus more than 48 h after the onset of CES [125]. Kohles et al. analyzed the meta-analysis and concluded that the methods of Ahn et al. were flawed and understated the value of early intervention [126]. Todd analyzed the data and concluded that patients treated less than 24 h after onset of CES were more likely to recover bladder function than those treated beyond 48 h [127]. Gleave and MacFarlane [128] and others [90, 123] subdivide CES into patients with complete denervation of the bladder and urinary sphincter (those with urinary retention and overflow incontinence) versus patients with incomplete

CES who have reduced urinary sensation, loss of the desire to void, or poor urinary stream, but who do not have urinary retention with overflow incontinence. Many of these authors believe that if the patient has urinary retention with overflow incontinence implying complete bladder denervation, urgent decompression of the cauda equina confers no benefit [90, 128]. Other authors have reported benefit from early surgery even in the complete CES group [123]. Other single-series reports did not find significant benefit from early operation [129–132]. Authors agree that better preoperative function predicts even better postoperative function.

Variables which confound evaluation include (1) the definition of CES and its onset (most authors define CES as when the patient develops sphincter or sexual dysfunction and perineal/perianal sensory loss), (2) determining completeness of bladder denervation, (3) demographic and epidemiologic factors including different clinical presentations, (4) pathologic features and the surgical procedure performed, and (5) timing and specifics of postoperative assessment.

CES is important to recognize and treat because it affects younger, working adults, and the aftermath can be devastating due to sensory and motor deficits, impaired sphincter control, and reduced sexual function. Even with prompt recognition and treatment, litigation can follow. Lavy et al. estimated that at least 10% of CES patients in England involve litigation [90]. CES due to a large disk should be considered as an emergency unless the patient presents with a leisurely and/or stable course. Operating within 24 h of the onset of sphincter trouble and perineal/perianal sensory disturbance is probably better than operating between 24 and 48 h, which is probably better than operating more than 48 h after onset, especially in patients with preserved bladder sphincter function. In general, this will mean that the patient who is diagnosed as having an acute or subacute CES should be referred directly to an emergency room that has the capability of performing MRI (the diagnostic imaging study of choice) and simultaneously arranging for emergency consultation with a spine surgeon. The benefit of emergency surgery needs to be balanced against operating in the middle of the night with a tired crew unfamiliar with the surgeon or procedure being performed.

Disk compression of a single lumbosacral nerve root is much more common than CES. Patients who present with LBP and severe weakness in the distribution of a single nerve root should be expeditiously evaluated, and many of these patients will come to surgery. Laminectomy and discectomy can aid in the recovery of a severely compressed lumbosacral nerve root. However, there is no evidence that outcomes from surgery for a single radiculopathy are better with emergent surgical intervention. Therefore, the patient with a single radiculopathy and a severe motor deficit due to spondylosis should be evaluated and treated urgently but not emergently. The urgency increases if a second nerve root is involved. Lumbar spinal stenosis, spondylolisthesis, and synovial cysts rarely present emergently. When they do, it is usually the result of a superimposed disk herniation or trauma.

Apart from CES or a severe monoradiculopathy, most patients presenting with spondylotic LBP with or without radicular pain should be treated conservatively. Current evidence-based guidelines for the evaluation and treatment of acute and chronic LBP are available (e.g., http://www.icsi.org) [18, 57, 133–138] (Figs. 2.11–2.14).

Traumatic Lower Spine Emergencies

In most instances, the patient whose lower spine pain is secondary to trauma will be able to describe, sometimes in vivid detail, their injury and current symptoms. However, there are some circumstances where this is not the case, such as (1) minor or no trauma in the patient with osteoporosis; (2) the patient is confused or unconscious due to a simultaneous head injury or drug or alcohol intoxication; (3) the patient has dementia, mental retardation, or a significant psychiatric illness; and (4) the patient has sustained an additional injury, such a long bone fracture, which distracts the patient's and provider's attention. There is also the situation where the injured patient has suffered a thoracolumbar fracture

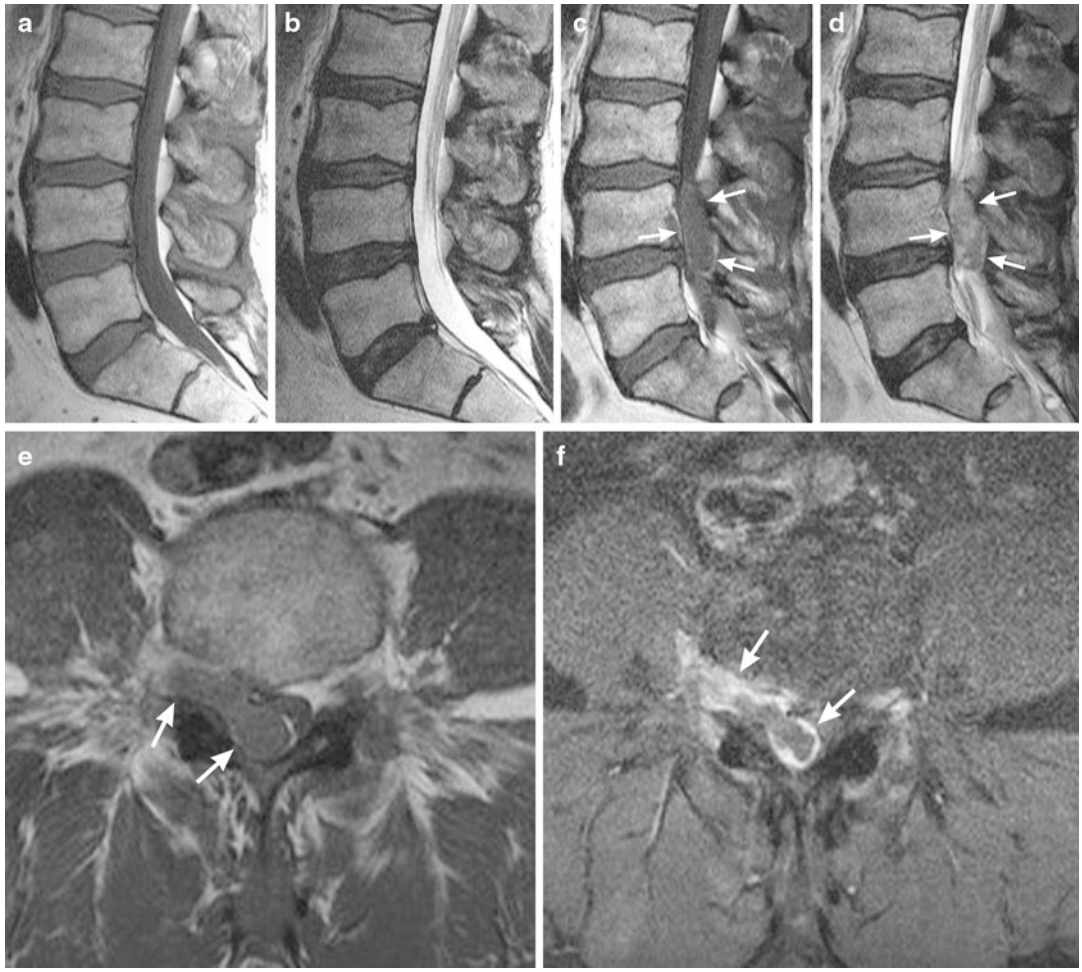

Fig. 2.11 Images of cauda equina compression due to a massive disk extrusion. A 55-year-old man presents with progressive back pain over 6 weeks. T1 (**a**)-weighted and T2 (**b**)-weighted sagittal MRI images early in his course show only mild disk degeneration with a widely patent central canal. An MRI, 6 weeks later when bilateral lower limb weakness and perineal numbness began, shows a large epidural process effacing the central canal on T1 (**c**)-weighted and T2 (**d**)-weighted images (see *arrows*). Axial pre (**e**)-contrast and post-contrast (**f**) T1-weighted images show a peripherally enhancing epidural process (see *arrows*) displacing the compressed thecal sac to the left. The radiologist's impression was a probable epidural abscess, but operation showed a massive disk extrusion

which is significant but has not as yet caused the patient any symptoms, nor produced any recognized signs on examination. This usually occurs in the setting of major trauma.

Vertebral compression fractures (VCF) are very common. There are an estimated 700,000 new cases of VCF each year in the USA [139]. They are usually due to osteoporosis, but some are due to a pathologic fracture secondary to an osteolytic tumor within the vertebra. Osteoporotic VCF typically affect the lower thoracic and lumbar spine. Most patients report some trauma as an inciting cause, but the trauma can be quite mild such as a fall on the buttocks or lifting an object, and a small number of patients report no injury. Plain X-rays, CT, MRI, and even radionuclide bone scanning can help in diagnosis. MRI can help to determine the age of the fracture by showing edema in the affected bone which typically lasts for at least 3–4 months but can last longer.

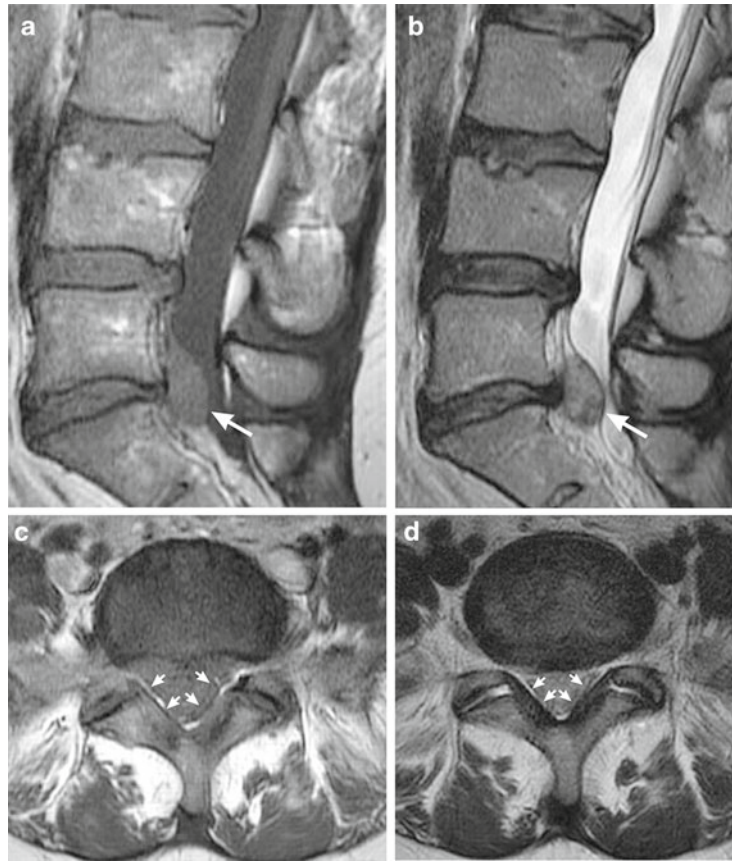

Fig. 2.12 Very large disk extrusion which caused sciatica without neurological deficit. A 44-year-old woman presents with left S1 radicular pain without neurological deficit. T1 (**a**)-weighted and T2 (**b**)-weighted sagittal MRI images and T1 (**c**)-weighted and T2 (**d**)-weighted axial MRI images at L5 show a large disk extrusion which severely effaces the thecal sac and compresses it against the left posterolateral spinal canal (see *arrows*). She was treated conservatively, and her sciatica eventually resolved. There is poor correlation between imaging findings and clinical presentation. Severe central canal narrowing on imaging does not always equate to neurological compromise

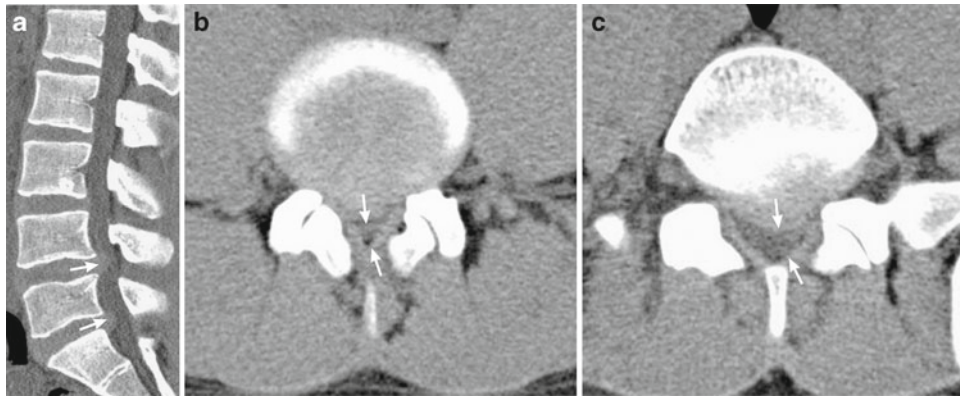

Fig. 2.13 Lumbar spinal canal stenosis. A 38-year-old man presents with progressive lower limb pain and numbness brought on by standing and walking. Sagittal CT reconstruction (**a**) and axial CT images at L4 (**b**) and L5 (**c**) show a congenitally narrow central canal due to short pedicles with superimposed disk protrusions at L4 and L5 (see *arrows* in **a**). The thecal sac is severely constricted and has a trefoil shape at the L4 interspace (see *arrows* in **b**) and more room at the level of the vertebral body (see *arrows* in **c**). This patient's lumbar spinal stenosis is currently being treated conservatively

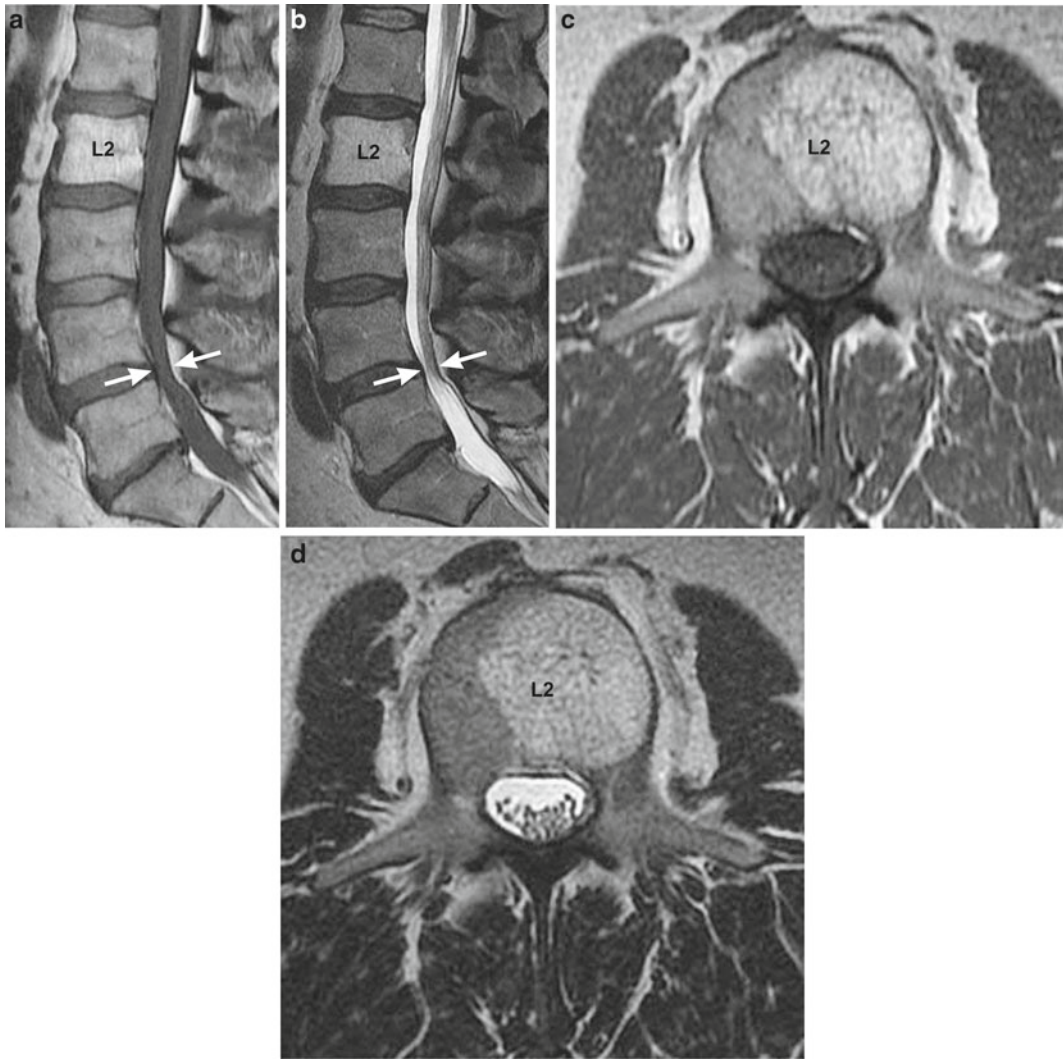

Fig. 2.14 Lumbar spinal canal stenosis. Sagittal T1 (**a**)-weighted and T2 (**b**)-weighted MRI images in a patient with low back pain demonstrate hyperintense T1 and T2 signal in the L2 vertebral body. Axial images at the L2 level with T1 (**c**) and T2 (**d**) weighting are confirmatory. This is the imaging appearance of a benign hemangioma of no clinical consequence. The T1 and T2 hyperintensity is due to the fat content of the lesion. Beware of being distracted from the truly significant finding which is the congenital central canal stenosis at L4–5 (*arrows* in **a** and **b**)

A minority of patients experience neurological symptoms due to bone fragment displacement into the spinal canal. For these patients, surgical intervention may be necessary. Bone densitometry is often obtained to confirm the presence of and gauge the severity of the patient's osteoporosis. Traditionally, patients with VCF were treated with analgesics, bracing, and activity modification. Percutaneous techniques of vertebral augmentation (vertebroplasty and kyphoplasty) have been used to treat painful VCF due to osteoporosis and tumor. Although these injections seem to provide patients with prompt pain relief, two recent double-blind, placebo-controlled trials failed to show benefit from vertebroplasty [140–142].

Conservative estimates suggest that more than one million blunt trauma patients with possible

associated spine injuries are seen annually in US emergency departments [143]. The incidence of thoracolumbar fracture following blunt trauma has been reported to be from 2% to 7.5% [44]. Thoracolumbar fractures are associated with neurological injury in 26–40% of patients [44].

Traumatic thoracolumbar spinal fractures are usually due to falls and motor vehicle accidents [44]. Indications for imaging the thoracolumbar spine in patients with trauma are reported to include: motor vehicle crash greater than 35 mph; fall from a height of greater than 15 ft; automobile hitting pedestrian with pedestrian thrown greater than 10 ft; assaulted with a depressed level of consciousness; a known cervical spine injury; and rigid spine disease (e.g., ankylosing spondylitis, diffuse idiopathic skeletal hyperostosis) [143]. Clinical signs found to be associated with thoracolumbar fracture include (1) back pain/midline tenderness (sensitivity 62.1%, specificity 91.5%), (2) palpable midline step (sensitivity 13.8%, specificity 100%), (3) back bruising (sensitivity 6.9%, specificity 98.6%), and (4) abnormal neurological signs (sensitivity 41.4%, specificity 95.8%) [44]. Neurological symptoms should probably be added to this list. Hsu et al. also reported that any lowering of the GCS (<15), alcohol or drug intoxication, and a major distracting injury can hinder one's assessment of the thoracolumbar spine and increase the need for imaging [44]. The presence of a cervical spine fracture doubles the risk of a thoracolumbar fracture [144]. In addition to injuring the spine proper, thoracolumbar trauma can also damage the aorta and spinal cord blood supply. Major thoracolumbar fracture types include wedge compression, burst, flexion-distraction (or seatbelt), and fracture-dislocation (which are typically highly unstable and usually associated with neurological injury) [145]. There are several classification systems for thoracolumbar fractures [146]. Penetrating spine trauma, most commonly a gunshot wound, is much less common. The thoracolumbar junction is the most common site for traumatic thoracolumbar fractures [24, 44]. Spine fractures are assessed for stability which is judged on a continuum. Patients with a possible spine fracture should be immobilized while they are transported, examined, and imaged.

Multidetector CT is the imaging procedure of choice for assessing the thoracolumbar spine. In patients who undergo CT of the torso (thorax–abdomen–pelvis), images can be reformatted to adequately assess the spine.

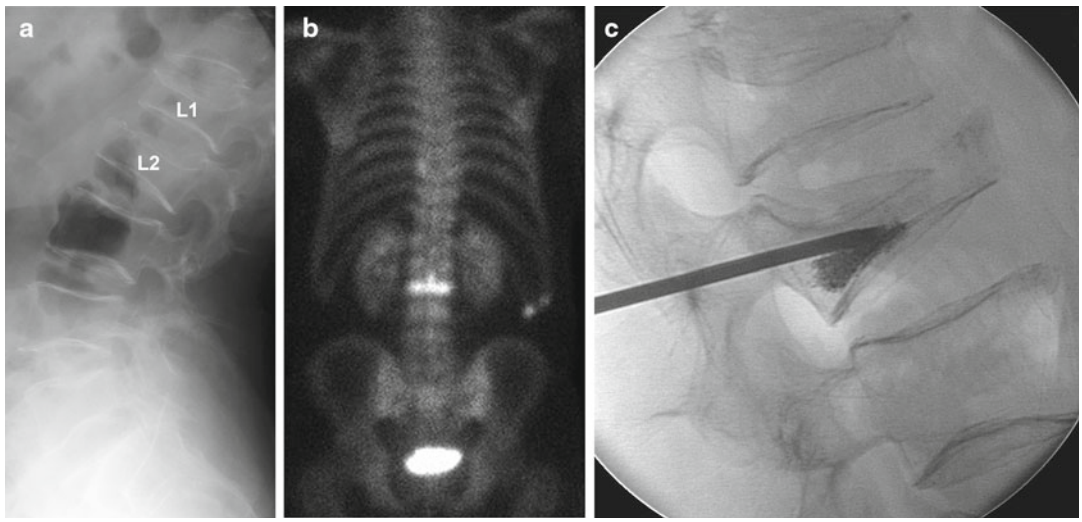

Fig. 2.15 Images of old and recent compression fractures. A 75-year-old man presents with acute upper lumbar pain following minimal trauma. A lateral radiograph (**a**) shows compression of the bodies of L1 and L2. There were no prior films for comparison. A radionuclide bone scan (**b**) shows increased activity at L2 only. L2 is the site of his acute fracture, while the L1 fracture is longstanding and asymptomatic. He was ultimately treated with bone augmentation (vertebroplasty) (**c**)

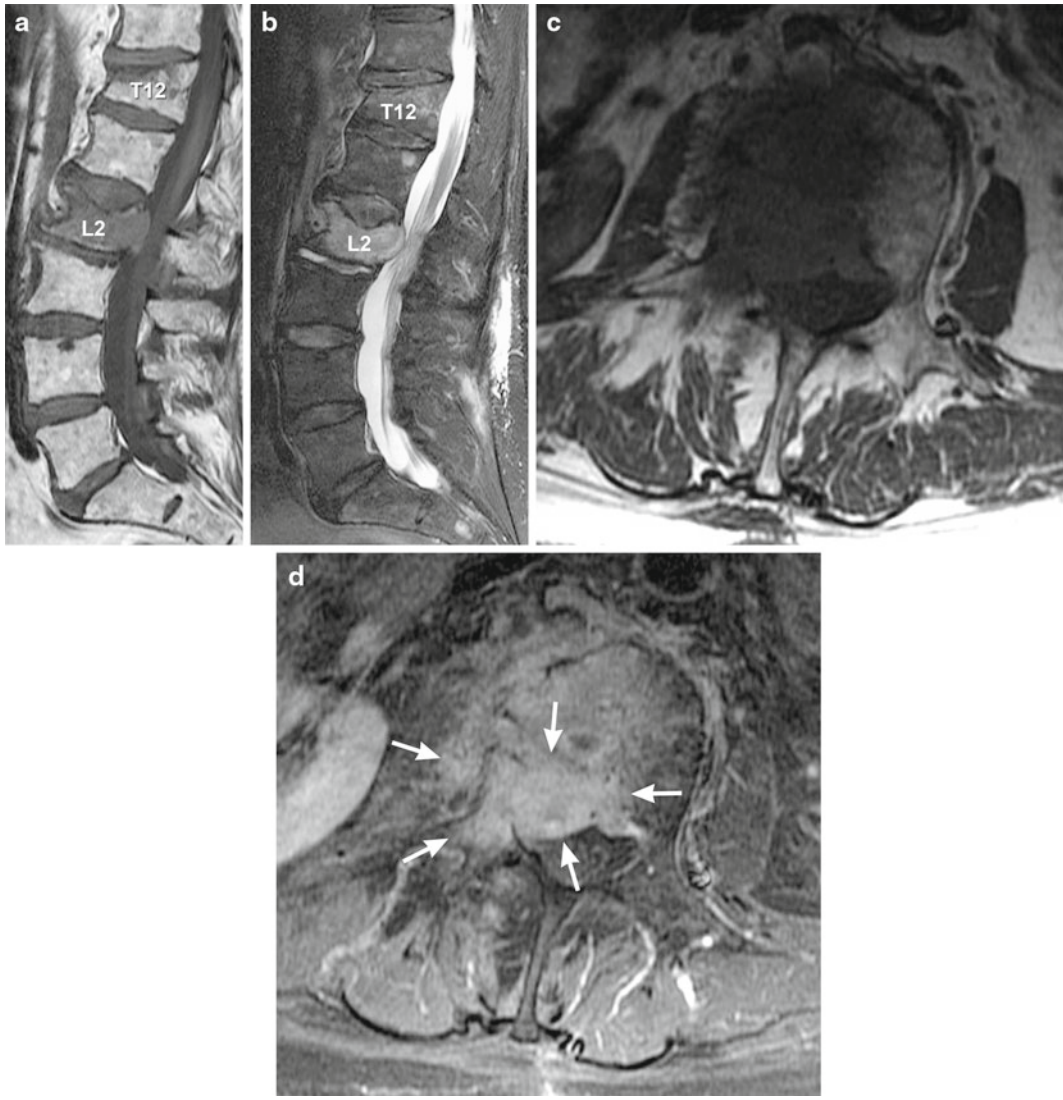

Fig. 2.16 Benign and malignant fractures. A 68-year-old woman presents with new low back pain and right groin and medial thigh pain. Sagittal T1 (**a**)-weighted and fat-saturated T2 (**b**)-weighted MRI images show a benign-appearing compression of the superior end plate of T12. Note that marrow signal change is restricted to the immediate sub-end-plate marrow. There is also a malignant, pathologic compression fracture of L2, and here the signal abnormality encompasses the entire vertebral body, which bulges posteriorly into the spinal canal. Axial pre (**c**)-contrast and post (**d**)-contrast-enhanced T1-weighted images at the L2 level show that the marrow signal abnormality extends from the vertebral body into the right pedicle, and there is enhancing tumor tissue which invades the epidural space and paraspinal soft tissue (see *arrows*)

MRI should be performed in patients who have possible spinal cord injuries secondary to bony compression, disk protrusion, spinal cord ischemia, or hematoma, and in patients with suspected ligamentous instability.

Fractures that are stable and usually without neural compression are typically managed conservatively with external bracing, while unstable injuries and many with neural compression may require surgical intervention and stabilization often with instrumentation (placement of metal hardware). The use of high-dose parenteral corticosteroids for nonpenetrating acute spinal cord injuries is controversial [147] (Figs. 2.15–2.17).

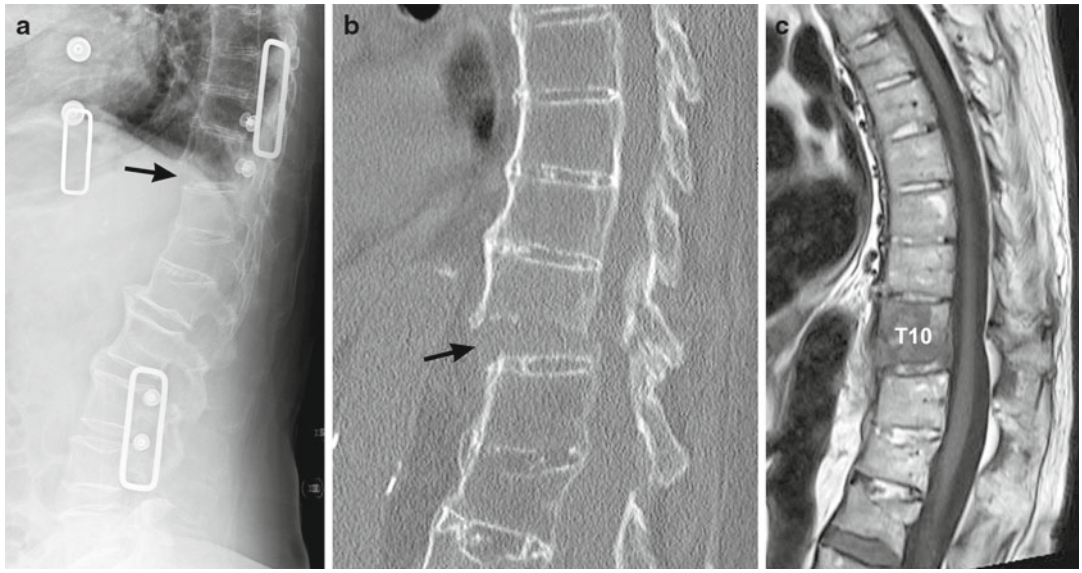

Fig. 2.17 Displaced vertebral fracture in a patient with a rigid spine. A 52-year-old man with known ankylosing spondylitis (AS) presents with low posterior thoracic pain following a low-impact motor vehicle accident. A lateral radiograph (**a**) while the patient is on a backboard demonstrates a displaced fracture through the inferior T10 vertebral body which is more conspicuous on a lateral CT reconstruction (**b**) (see *arrows*). Marrow edema is noted throughout the T10 vertebral body on sagittal T1-weighted MRI (**c**). Any process rendering the spine unusually stiff (e.g., AS, diffuse idiopathic skeletal hyperostosis [DISH]) predisposes to catastrophic fracture with modest trauma

Conclusions

Some patients who present with LBP clearly have an emergent condition. Consider the patient with LBP after a high-speed motor vehicle accident or the patient with or without sepsis who presents with a rapidly progressive cauda equina syndrome. These patients require emergent assessment and treatment. Less obvious is the patient with acute or subacute LBP who is seen in the outpatient setting. These patients may have an urgent or soon-to-be-emergent condition which will blossom if not recognized. A search for red flags in the history and on careful physical and neurological examinations should identify the patient who is likely to harbor a serious condition, such as infection, tumor, aortic dissection or aneurysm, large lumbosacral disk, or traumatic spinal injury. Patients identified by this process require expeditious investigation and, depending upon the results, possible urgent intervention. MRI is the best imaging study for most of the worrisome causes of LBP such as infection, tumor, and spondylosis. CT and ultrasound are the preferred imaging modalities for TAD and AAA, respectively. CT can help "clear the spine" in patients with a history of trauma, and aid in the diagnosis of other low back emergencies.

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Dizziness and Vertigo Presentations in the Emergency Department

3

Kevin A. Kerber and Robert W. Baloh

Abstract

Dizziness and vertigo are common reasons that patients present to the emergency department. Most patients have benign or self-limited causes, but a small proportion harbor a dangerous disorder such as ischemic stroke. In this chapter, we highlight the critical steps in evaluating and managing patients who present with dizziness symptoms in the emergency setting. We focus on the symptom of vertigo and distinguishing peripheral vestibular from central vestibular disorders.

Keywords

Dizziness • Vertigo • Vestibular neuritis • Benign paroxysmal positional vertigo • Stroke • Meniere's disease

Introduction

Physicians have high levels of uncertainty when faced with the evaluation and management of dizziness presentations in the emergency setting. In a recent survey of emergency medicine physicians, "identification of central or serious causes of vertigo" was ranked as the #1 priority for clinical decision support research in adult emergency presentations [1]. Uncertainty also likely contributes to the dramatic increase in the use of imaging studies in emergency department dizziness presentations. In 1995, less than 10% of patients presenting to emergency departments (ED) with dizziness were evaluated with a head computerized tomography (CT) scan, but by 2004 the rate had doubled to greater than 25% [2]. Despite this increase in head CT use, the proportion of ED dizziness visits receiving a central nervous system diagnosis did not increase [2].

Most patients presenting with dizziness can be rapidly assessed and valid estimates can be made regarding diagnostic possibilities—thus informing management decisions. There already exist many effective treatments for dizziness symptoms and specific dizziness disorders. In fact, benign paroxysmal positional vertigo (BPPV) is

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Table 3.1 The three most common specific peripheral vestibular disorders

	Type of presentation	Symptoms	Exam findings	Red flags for central etiology[a]
Vestibular neuritis	Acute severe prolonged dizziness	Constant vertigo, nausea, and imbalance	Spontaneous unidirectional horizontal nystagmus, positive corresponding head thrust test[b]	Central pattern of nystagmus[c]. Negative head thrust test
Meniere's disease	Recurrent spontaneous attacks	Vertigo, nausea, imbalance lasting hours, unilateral fluctuating hearing loss	Peripheral pattern of nystagmus, unilateral hearing loss	New onset, crescendo attacks lasting minutes, central patterns of nystagmus[c]
Benign paroxysmal positional vertigo	Recurrent positionally triggered attacks	Recurrent positionally triggered attacks of vertigo Duration <1 min	Positional testing Dix Hallpike test triggers burst of upbeat torsional nystagmus[d]	Central pattern of nystagmus[c], nonresponse to repositioning maneuvers

[a]Red flags for all presentation type include other focal neurological signs or symptoms.
[b]With left-sided vestibular neuritis, the spontaneous nystagmus beats to the right side and the head thrust test reveals a corrective saccade after movements to the left side.
[c]Central patterns of nystagmus include spontaneous vertical (up or downbeating) nystagmus, bidirectional gaze-evoked nystagmus, and downbeating nystagmus triggered by positional testing.
[d]Benign paroxysmal positional vertigo (BPPV) variant: with horizontal canal BPPV, horizontal nystagmus will be triggered by supine positional testing.

among the most common causes of dizziness and it can be cured by a simple repositioning maneuver (i.e., the Epley maneuver) at the bedside [3]. The goal in the management of dizziness presentations is to get the most effective treatments to the dizziness patients most likely to benefit from them, and to do so in an efficient manner. Achieving this goal depends on the bedside assessment and the formulation of the case.

Most of the uncertainty in dizziness presentations occurs when attempting to distinguish "peripheral" (and generally benign) from "central" (and potentially life-threatening) causes. The key to distinguishing between these is understanding the three most common peripheral vestibular disorders (i.e., vestibular neuritis, BPPV, and Meniere's disease) (Table 3.1). Typically, the most effective way to "rule out" a life-threatening central disorder is to "rule in" a specific peripheral vestibular disorder. The peripheral vestibular disorders are important because they account for a large proportion of the causes of dizziness, present with highly stereotyped characteristics, and can be effectively treated. The time to consider a central etiology is when the presentation deviates from the stereotyped characteristics of the specific peripheral vestibular disorders.

In this chapter, we highlight the critical steps in evaluating and managing patients who present with dizziness symptoms in the emergency setting. We focus on the symptom of vertigo and distinguishing peripheral vestibular from central vestibular disorders.

Evaluation of Emergency Presentations

The effective clinical evaluation of patients presenting with dizziness in the emergency setting requires an organized approach that allows the physician to gather all of the most relevant information and then to formulate the case in a way that establishes the most likely cause and identifies any relevant "red flags" that could suggest a central disorder.

Step 1. Determine if the Dizziness Is the Principal Symptom as Opposed to a Minor Accompanying Symptom

Dizziness is an incredibly common accompanying symptom. More than 60% of all patients in the emergency department will report having

dizziness when specifically queried about it [4], and in most cases it is a minor accompanying symptom rather than the principal symptom. One of the main problems with dizziness presentations is that the patient's descriptions of dizziness can be very vague, inconsistent, and unreliable [4]. So prior to focusing all attention on the dizziness symptom, first consider if other symptoms are more prominent. For example, if chest pain is the principal symptom, then an initial focus on cardiac etiologies is probably more effective than a focus on vestibular system etiologies.

Step 2. Define the Characteristics of the Dizziness Symptom

If the dizziness symptom is the principal symptom, then the next step is to more clearly define it. However, defining the dizziness symptom is often not a simple task because it is a subjective experience and many patients with dizziness have difficulty describing what they are actually experiencing. There can also be problems with being overly reliant on the patient's description of the symptom in informing the potential causes. For example, vertigo (i.e., visualized movement of the environment) is one common type of dizziness symptom, and it should localize to the vestibular system (either the peripheral vestibular system or the central vestibular system). But some patients with cardiac disorders unlikely to involve the vestibular system will report movement of the environment particularly if they are specifically queried about it [5]. An intense visualized room-spinning sensation is a much more valid indicator of a vestibular system disorder than either an "internal" spinning sensation (i.e., no actual spinning of the environment) or a very mild visualized spinning sensation. There are also patients who have a clear vestibular disorder, but who describe the symptom as a nonvertiginous vague type of dizziness, even in the setting of frank nystagmus.

Other types of dizziness symptoms to consider are light-headedness with presyncope, light-headedness (or similar "head" sensation) without presyncope, or imbalance. Some patients will use the label "dizziness" to describe anxiety-like symptoms, general fatigue or weakness, or just not feeling well.

Because of the problem with patient descriptions of dizziness symptoms, in many cases the characteristics of the symptom may be equally or even more important than defining the exact symptom itself. Defining the characteristics of the symptom starts with defining whether the symptom is episodic or constant. If the symptom is episodic, then one should probe regarding triggers of the symptom and the frequency and duration of the episodes. When the symptom is constant, one should determine the onset of the symptom and aggravating and alleviating factors. Determining accompanying symptoms is also a vital step, particularly gathering information about auditory symptoms or focal neurological symptoms.

The information from the history will eventually be a key aspect when formulating the case (see step 5). The details from the history help to categorize the patient into broad classifications of dizziness presentations which are relevant to determining potential etiologies. Helpful classifications of presentations include the following: acute severe prolonged dizziness, recurrent spontaneous dizziness attacks, and recurrent positionally triggered dizziness attacks. The type of presentation is determined based on the details of the history of present illness. Acute severe prolonged dizziness is the sudden onset of a constant symptom that is generally a debilitating symptom. Recurrent spontaneous dizziness attacks are reported by patients who have had at least several attacks that come on without any apparent inciting event. Recurrent positionally triggered dizziness attacks consist of the symptom triggered by certain head movements.

Step 3. Perform a General Neurological Examination

A general neurological examination is important because any relevant motor, sensory, or language deficits will likely warrant a workup for a central disorder regardless of the other characteristics of

Table 3.2 Patterns of nystagmus associated with the type of dizziness presentation

	Spontaneous nystagmus?	Peripheral vestibular patterns of nystagmus	Central vestibular patterns of nystagmus
Acute severe prolonged dizziness	Yes	• Unidirectional, horizontal spontaneous[a]	• Direction-changing, gaze-evoked[b] • Spontaneous vertical or pure torsional
Recurrent spontaneous attacks	Yes/No[c]	• Unidirectional, horizontal spontaneous[a]	• Direction-changing, gaze-evoked[b] • Spontaneous vertical or pure torsional
Recurrent positionally triggered attacks	No	• *Dix–Hallpike test*: burst of upbeat torsional[d] • *Supine positional test*: horizontal nystagmus with direction of nystagmus changing with head movement to opposite side[e]	• Downbeating persistent • Pure torsional

[a]Pattern can less commonly be caused by central lesions, increasing the importance of assessing risk for central lesion and the results of the head thrust test.
[b]Example of direction-changing gaze-evoked nystagmus: left-beating nystagmus with gaze to the left; then, right-beating nystagmus with gaze to the right.
[c]May not have nystagmus if evaluation takes place in between attacks.
[d]Upon sitting up from Dix–Hallpike test, a burst of downbeating torsional nystagmus will often be triggered. Thus, a direction-changing positionally evoked nystagmus.
[e]In rare circumstances, pattern can be caused by a central lesion.

the dizziness symptom. This is because peripheral vestibular disorders and general medical disorders will not cause focal neurological deficits. Unilateral hearing loss, on the other hand, will strongly suggest a peripheral etiology.

For similar reasons, a general medical examination can also be important when trying to exclude a general medical disorder such as a heart arrhythmia or orthostatic hypertension.

Step 4. Perform a Neuro-Otologic Assessment

If the source of the symptom is not clear after performing steps 1–3, then the neuro-otologic assessment becomes paramount. Subtle differences in eye movements or the vestibuloocular reflex can be highly localizing. The key neuro-otologic examination components are the following: an assessment of nystagmus, positional testing when applicable, and the head thrust test when applicable.

Pathological nystagmus occurs as the result of an acute imbalance of the vestibular system which can stem from a lesion (or aberrant stimulation) of peripheral or central vestibular structures. Most physicians notice when nystagmus is present, but it is the pattern of nystagmus—not the mere presence—that is important for discriminating a peripheral lesion from a central lesion. The localizing value of the pattern of nystagmus is also dependent on the type of presentation. Some general rules about the localizing value of nystagmus apply (Table 3.2). In patients with acute severe prolonged vertigo, a unidirectional spontaneous horizontal nystagmus is highly suggestive of a lesion of the vestibular nerve. The lesioned side is the side opposite the direction of the fast phase of nystagmus. Unidirectional spontaneous nystagmus implies that the nystagmus is present in primary gaze and that the nystagmus never changes direction. For example, if nystagmus beats to the left side, then it should never transition to beating to the right side. The left-beating nystagmus does increase in velocity when the patient looks to the left side and also decrease (or stop) when the patient looks to the right side, but it will not transit to a right-beating nystagmus if the lesion is on the vestibular nerve. A central

lesion is presumed in acute severe vertigo presentations whenever a pattern other than unidirectional horizontal nystagmus is observed. The most common central nervous system patterns of nystagmus in acute severe vertigo presentations are direction-changing gaze-evoked nystagmus (i.e., patient looks to the right and nystagmus beats to the right; then, patient looks to the left and nystagmus beats to the left) and spontaneous vertical (typically downbeating) nystagmus.

Positional testing is an important component of the bedside examination when the type of presentation is recurrent positional dizziness. It is important to note that the patterns of nystagmus that discriminate peripheral from central etiologies when the presentation type is recurrent positional dizziness are different from the patterns in acute severe dizziness presentations. Generally no spontaneous nystagmus is present in positionally triggered dizziness presentations. In positionally triggered attacks caused by BPPV, the nystagmus can change direction, which occurs with changes in head position. In addition, a principally vertical nystagmus is the characteristic pattern of the most common BPPV variant (i.e., posterior canal BPPV). In posterior canal BPPV, the Dix–Hallpike test (Fig. 3.1) [3, 6] triggers a burst of upbeating and torsional nystagmus which lasts less than 1 min. If the patient were to next sit back up from the Dix–Hallpike position, then a burst of downbeating and torsional nystagmus is triggered. The reason for the change in direction of the nystagmus after sitting up is that the particles move in the opposite direction after sitting up compared to the head-hanging (i.e., Dix–Hallpike) position. However, if persistent downbeating nystagmus is triggered by the Dix–Hallpike test, then a central nervous system lesion is presumed.

If the Dix–Hallpike positional test does not trigger the nystagmus of BPPV, then supine positional testing is used to test for the less common horizontal canal variant of BPPV [7]. With this test the patient lies supine and the head is turned first to one side and held for at least 30 s and then to the other side and held for the same duration. A burst of horizontal nystagmus beating toward the ground is characteristic of the horizontal canal variant of BPPV. The side with stronger nystagmus is the abnormal side. More persistent nystagmus beating away from the ground can occur if the debris is stuck within the canal or is attached to the cupula [3, 7].

The head thrust test is an important bedside examination component when the type of dizziness presentation is acute severe dizziness (Fig. 3.2). The head thrust test allows a direct assessment of the vestibular-ocular reflex (VOR) and an abnormal result is highly suggestive of a vestibular nerve lesion [8, 9]. This test is different from the doll's eye test because the doll's eye test uses slow rotation of the head to either side, whereas the head thrust test uses quick movements which isolate the vestibular system function. The corresponding eye movements of the doll's eye test can be generated by either the vestibular system or the smooth pursuit system in a conscious patient. But only the vestibular system generates the reflex movement of the eyes after the quick movement of the head thrust test (the smooth pursuit system only works at low stimulus velocities). To test the VOR using the head thrust test, the examiner stands in front of the patient and holds the patient's head with both hands. The patient is instructed to focus on the examiner's nose, and then the examiner initiates a quick 10–15° movement of the patient's head to one side. When there is a lesion of the VOR on one side, a corrective eye movement (i.e., a corrective "saccade") back to the examiner's nose is seen after the head is moved toward the affected side. In contrast and serving as an internal control, the eyes will stay on target (i.e., the examiner's nose) after the head thrust test toward the normal side because the VOR is intact on that side. These features can be appreciated even when spontaneous nystagmus is present. The reason for the corrective saccade with a peripheral vestibular lesion is rooted in the physiology of the vestibular system [10]. When the head is moved quickly in one direction, the reflex (i.e., the VOR) that moves the eyes toward the opposite direction is generated mostly by the side the head moved toward. Thus a patient with vestibular neuritis of the right side will present with a

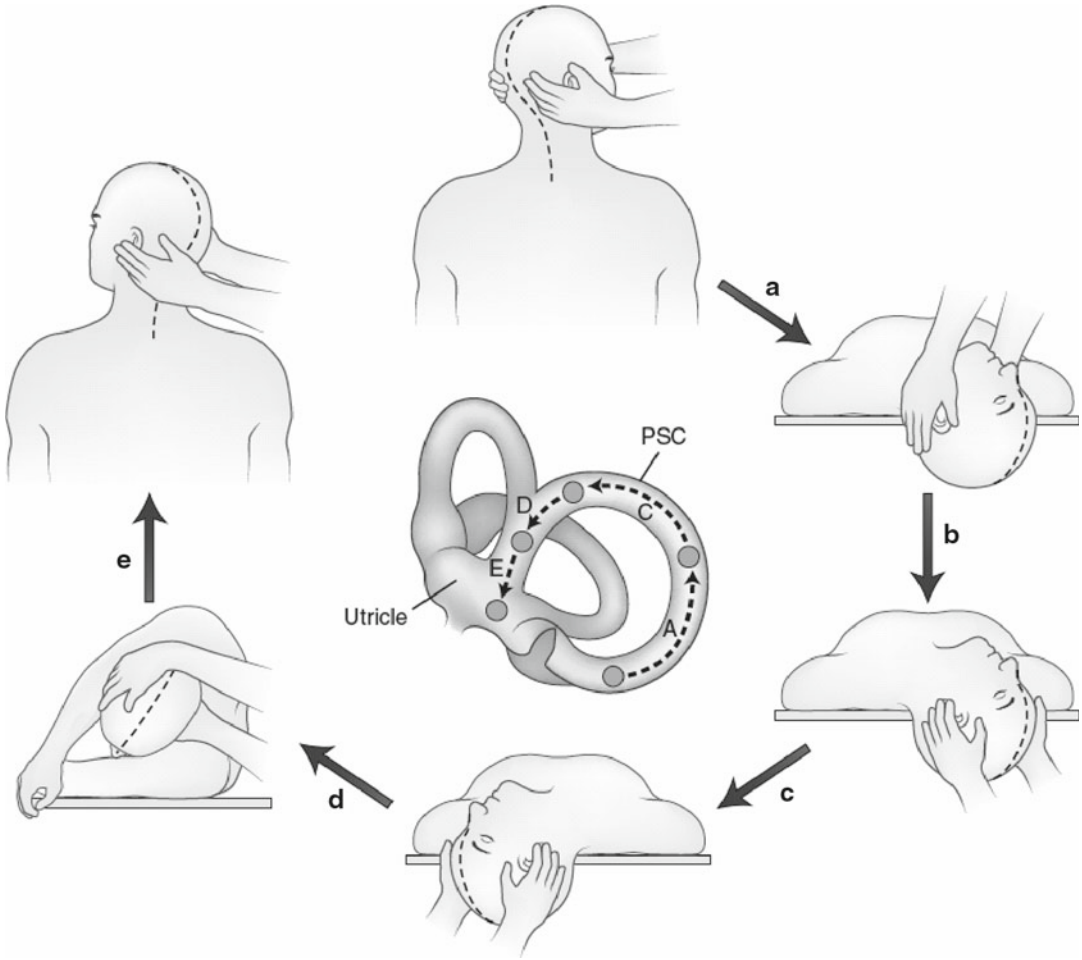

Fig. 3.1 The Dix–Hallpike test for the diagnosis of posterior canal benign paroxysmal positional vertigo affected the right ear, and the Epley maneuver for the treatment of posterior canal benign paroxysmal positional vertigo affecting the right ear. The procedure can be reversed for treating the left ear. The drawing of the labyrinth in the center shows the position of the debris as it moves around the posterior semicircular canal (PSC) and into the utricle (UT). The patient is seated upright, with head facing the examiner, who is standing on the right. (**a**) The patient is then rapidly moved to head-hanging right position (Dix–Hallpike test). This position is maintained until the nystagmus ceases. (**b**) The examiner moves to the head of the table, repositioning hands as shown. (**c**) The head is rotated quickly to the left with right ear upward. This position is maintained for 30 s. (**d**) The patient rolls onto the left side while the examiner rapidly rotates the head leftward until the nose is directed toward the floor. This position is then held for 30 s. (**e**) The patient is rapidly lifted into the sitting position, now facing left. The entire sequence should be repeated until no nystagmus can be elicited. Following the maneuver, the patient is instructed to avoid head hanging positions to prevent the debris from reentering the posterior canal. From: Rakel RE. Conn's Current Therapy 1995, p. 839, WB Saunders, 1995. Used with kind permission of Elsevier. Video clips of the Dix–Hallpike test, Epley maneuver, and other positional test are available from the American Academy of Neurology at http://www.neurology.org/cgi/content/full/70/22/2067/DC2

left-beating unidirectional nystagmus and the head thrust test will be positive with movement toward the right side.

The neuro-otologic examination of the patient with dizziness caused by Meniere's disease is less predictable because most of the symptoms have typically resolved by the time of the evaluation, the nystagmus can be either toward or away from the affected ear (since it can be a stimulatory or inhibitory lesion),

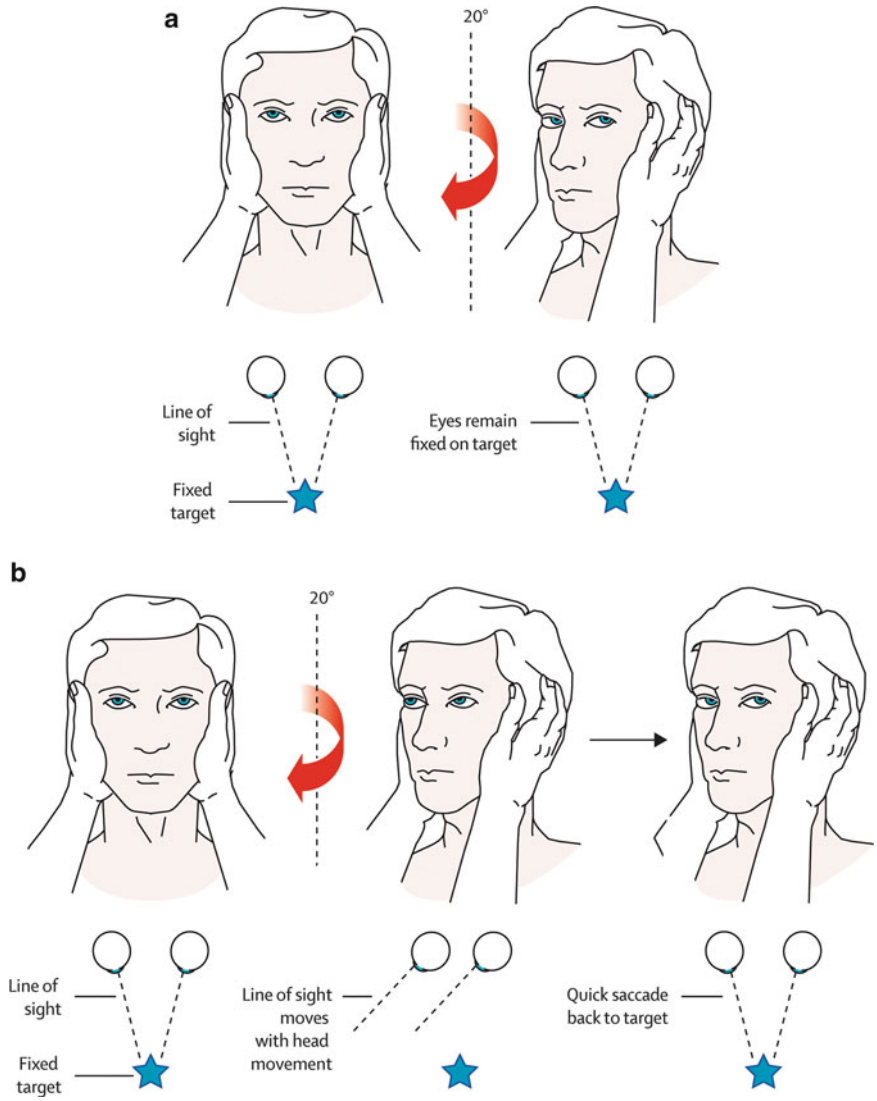

Fig. 3.2 The head thrust test. The head thrust test is a test of vestibular function that can be easily done during the bedside examination. This maneuver tests the vestibuloocular reflex (VOR). The patient sits in front of the examiner and the examiner holds the patient's head steady in the midline. The patient is instructed to maintain gaze on the nose of the examiner. The examiner then quickly turns the patient's head about 10–15 degrees to one side and observes the ability of the patient to keep the eyes locked on the examiner's nose. If the patient's eyes stay locked on the examiner's nose (i.e., no corrective saccade) (*picture* **a**), then the *peripheral vestibular system is assumed to be intact*. Thus, in a patient with acute dizziness, this finding suggests a central nervous system localization. If, however, the patient's eyes move with the head (*picture* **b**) and then the patient makes a voluntary eye movement back to the examiner's nose (i.e., corrective saccade), then this *suggests a lesion of the peripheral vestibular system and not the central nervous system*. Thus when a patient presents with the acute vestibular syndrome, the test result shown in *picture* **a** would suggest a central nervous system lesion, whereas the test result in *picture* **b** would suggest a peripheral vestibular lesion (thus, vestibular neuritis). From: Edlow JA, et al. Lancet Neurology 2008; 7(10):951–964. Used with kind permission of Elsevier

and the head thrust test is typically normal. Regardless, central patterns of nystagmus should be a red flag. Furthermore, a key feature of Meniere's disease is fluctuating hearing loss; however, the auditory symptoms can be mild or unappreciated by the patient during the early phases of the disorder. By mid-to-late stages of the disorder, a persistent unilateral hearing loss will be present.

Step 5: Formulate the Differential Diagnosis

When formulating the case, an initial helpful step is to first determine which classification of dizziness presentation the patient falls under. Likely etiologies can then be determined by further considering the presentation features and the information gathered from the examination.

Acute Severe Prolonged Vertigo

Vestibular neuritis is the most common cause of acute severe prolonged vertigo [11]. It is caused by a viral inflammation of the eighth cranial nerve and vestibular end organs. Vertigo is accompanied by severe nausea, vomiting, and imbalance. Patients will often describe the need to hold onto objects when walking or may even need to crawl. Typically hearing is not affected, but if it is, then the virus likely involves both auditory and vestibular components, so-called labyrinthitis. As noted earlier, the hallmark examination signs of vestibular neuritis are a spontaneous unidirectional horizontal nystagmus and a positive head thrust test to the side opposite the fasting beating component of the nystagmus.

Patients with vestibular neuritis are typically debilitated for the first day. Then, the natural history of the disorder is a gradual recovery over weeks to months. Vestibular physical therapy programs can help to speed the recovery [12]. In addition, the use of a burst and taper of oral corticosteroids can improve the recovery of the affected vestibular system as measured by the laboratory caloric response [13].

In any patient who presents with acute severe vertigo, stroke diagnosis should be considered. Stroke is an obvious concern when the patient reports other focal neurological symptoms or has other focal neurological signs. Though the likelihood of stroke diagnosis drops substantially when the patient presents with isolated vertigo (i.e., no symptoms other than vertigo, nausea, and imbalance) [14], case reports now demonstrate just how closely stroke can mimic vestibular neuritis [15–17]. Lacking is a formal validated tool to assess the probability of stroke in acute severe vertigo presentations. However, recently published research does help to assess bedside risk of stroke in acute dizziness presentations. From epidemiological study designs, the risk of stroke etiology among patients presenting to the ED with dizziness symptoms is about 3% [14]. If the dizziness is an isolated symptom, then the risk of stroke etiology drops to less than 1% [14]. However, the population of this study was patients with any dizziness symptom presentation, not just the acute severe vertigo presentation. This distinction is important because the probability of stroke is highest for acute severe vertigo presentations compared to the other types of dizziness presentations. One series that looked at acute vertigo presentations found a 25% (6 out of 24 patients) rate of stroke diagnosis [18]. Another series found that 25 out of 33 patients (76%) with acute severe vertigo presentations had stroke etiology, though a higher rate of stroke was selected for since at least one stroke risk factor was required for inclusion and a recent viral infection was an exclusion criterion [16]. In addition, patients in this series were enrolled even if they had bidirectional gaze-evoked nystagmus (a central pattern of nystagmus) at the time of presentation [16]. Even in these series which showed very concerning rates of stroke among acute severe vertigo presentations, the rate of stroke etiology dropped substantially among patients with isolated dizziness, unidirectional spontaneous horizontal nystagmus, and a corresponding positive head thrust test. Despite this, we still need large studies of the patients with acute severe vertigo so that validated and clinically meaningful probabilities can inform decisions.

Recurrent Spontaneous Attacks of Vertigo

Meniere's disease is the prototypical episodic otological disorder characterized by recurrent vertigo attacks (typically lasting hours). Overall, the prevalence of Meniere's disease in the general population is low [19]. In addition, Meniere's disease patients are probably less likely to present to the ED during acute attacks compared to those with the first ever acute severe vertigo attack. The reason may be that Meniere's disease attacks are typically limited to a couple of hours and patients learn over time that the attacks resolve with rest. To make the diagnosis of Meniere's disease requires the presence of a unilateral hearing loss which is typically a fluctuating symptom early in the course but then later becomes a fixed and progressive feature. Other auditory symptoms are also common, including unilateral tinnitus (typically a low roaring sound rather than a high-pitched sound) or bothersome pressure in one ear. The examination in patients with Meniere's disease can be variable in the acute setting because nystagmus can be caused by either stimulation or inhibition of the affected side. But a central pattern of nystagmus (e.g., spontaneous downbeating nystagmus or bidirectional gaze-evoked nystagmus) would be a reason for a workup for a central disorder. Patients with Meniere's disease do not typically have a positive head thrust test.

Migraine is a more common cause of recurrent attacks of vertigo (so-called migrainous vertigo). Attacks can last from minutes to hours and during attacks patients may exhibit features of both peripheral and central spontaneous and positional vertigo [20]. In between episodes, the exam is normal. The diagnosis rests on identifying other migraine symptoms (headache, aura, photophobia, phonophobia) with at least some attacks [21], but if a patient has recurrent vertigo attacks without hearing loss over time, then the most likely diagnosis remains migraine even if other migraine symptoms are not reported.

Transient ischemic attacks should be considered when brief vertigo attacks (minutes) occur in a patient with vascular risk factors. Usually at least some attacks are accompanied by other neurological symptoms, and they may have a crescendo-like presentation. Sometimes patients who eventually suffer a posterior circulation stroke can have isolated transient vertigo episodes preceding the stroke [22]. As with stroke in general, auditory symptoms can accompany the vertigo symptoms if the anterior inferior cerebellar artery is involved.

Recurrent Positionally Triggered Attacks of Vertigo

BPPV is the most common cause of positionally triggered vertigo and in fact is also believed to be the most common cause of vertigo in general [23]. BPPV can be cured at the bedside with a simple repositioning maneuver [24]. Thus, the ability to identify and treat BPPV is a major step not only for improving patient outcomes, but also for reducing unnecessary tests. The key feature of the history is that the episodes are triggered by head movements, not simply worsened by head movements. It is important to know that dizziness of any cause can worsen after certain position changes. But for patients with BPPV, the vertigo attacks are *triggered* by position changes. The patient with constant vertigo who reports that the symptom is better in certain positions and worse with movement should be classified as having acute severe prolonged vertigo rather than recurrent positionally triggered vertigo. The history of the patient with BPPV is vertigo triggered by head tilts (reaching for something on a high shelf), rolling over in bed, or getting in/out of bed. The vertigo attacks last less than 1 min, followed by a return to the normal state. Some patients will report attacks only in the morning or evening when getting in or out of bed, but others will report attacks throughout the day.

BPPV is caused by calcium carbonate crystals which are free floating in a semicircular canal, typically the posterior canal. The debris breaks from the otolith membrane for reasons that are not clear. This can occur as the result of head trauma, but typically occurs spontaneously (particularly with aging). When the particles enter the posterior canal they can become trapped and move back and

forth with position changes. Since the particles settle quickly after the movement, the symptoms and nystagmus last for only a brief period of time (<1 min). The particles can less commonly enter the horizontal canal and rarely even the anterior canal. The pattern of nystagmus is different depending on which canal is affected [25]. When the particles are in the posterior canal, a burst of upbeat and torsional nystagmus is seen after the patient is placed in the Dix–Hallpike position with the head turned toward the affected side (see Fig. 3.1) [6]. The nystagmus typically lasts only about 20–30 s. When the particles are in the horizontal canal, the nystagmus is horizontal and typically beats toward the ground after turning the head to either side while the patient is supine. The horizontal canal nystagmus lasts longer than the posterior canal nystagmus (as long as a minute) and can persist when the patient returns to the sitting position.

Central disorders can cause positional vertigo attacks, but the attacks typically have features that distinguish them from attacks in BPPV. A downbeating positional nystagmus is the most common pattern of nystagmus indicating a central localization—typically a midline cerebellar lesion. Downbeating positional nystagmus can be caused by the anterior canal variant of BPPV, but this variant is rare. Multiple sclerosis can also cause various types of positional nystagmus as can any other lesion involving central vestibular pathways in the brainstem or cerebellum. Importantly, central lesions do not cause the characteristic vertical torsional nystagmus pattern of posterior canal BPPV. However, central lesions—particularly lesions around the fourth ventricle—may cause a pattern of nystagmus similar to the pattern seen with horizontal canal BPPV [26]. Thus, a central lesion should be considered when a patient with the horizontal canal BPPV pattern of nystagmus has atypical features or is refractory to repositioning.

Other Dizziness Symptoms and Presentations

In the ED setting, the symptom of imbalance is associated with a higher odds of stroke diagnosis compared to the symptom of "dizziness" [14]. In stroke patients with imbalance, the lesion is typically in the midline or superior cerebellum and often the patient requires assistance to ambulate, if ambulation is possible at all [15, 27]. Since the lesions are often in the midline cerebellum, appendicular ataxia may be lacking. Some patients with dizziness in the emergency room will present with a chronic constant dizziness presentation rather than one of the three common presentation types described previously. If the neurological exam is normal in the patient with chronic dizziness, then the chance of a structural neurological disorder is very low. Migraine is the great mimicker of all causes of dizziness [20]. Symptoms in migraine can present as an acute severe attack, positional episodes, recurrent spontaneous attacks, or chronic constant symptoms. An accompanying headache occurs in less than 50% of the presentations, although a personal history of migraine headaches or a strong family history of migraine is common. Suggested diagnostic criteria require migraine symptoms with at least some attacks of vertigo [21, 28]. Unfortunately, the diagnosis of migraine remains a diagnosis of exclusion. Thus, if the symptom is new in onset and does not fit the features of a specific peripheral vestibular disorder, then serious central causes should be considered. However, if the symptoms have been present for at least a couple of months and the neurological exam is nonfocal, then the chance of uncovering a causative structural lesion of the central nervous system is very low.

Panic disorder and anxiety disorder often have dizziness or even vertigo as a symptom. Common accompaniments of these psychiatric disorders are a sense of doom or fear, heart palpitations, shortness of breath, and nonfocal numbness and tingling.

General medical disorders can cause various types of dizziness presentations. The dizziness is typically described as light-headedness. Processes that result in transient drops in blood pressure are probably the most common general medical causes of dizziness. Medication side effects or metabolic derangements should also be considered in the differential diagnosis.

Management of Emergency Presentations

The goal in the emergency setting is to stabilize symptoms and identify treatable disorders or monitor those patients at risk for worsening. Proceeding through the above steps will help to identify the most likely causes and red flags. Simply classifying the presentation as a "peripheral" cause or "dizziness not otherwise specified," without proceeding through the above steps, probably leaves too much room for error [29]. BPPV is not only readily identifiable at the time of the clinical presentation, but the most common type (i.e., posterior canal BPPV) can be effectively treated with the Epley maneuver (see Fig. 3.1) [3, 6, 30]. BPPV is unique in clinical medicine because not only can an accurate assessment of the likelihood of the diagnosis be made, but also you can take this one step further and actually prove the diagnosis at the bedside by treating it in a matter of minutes. If the features are atypical for BPPV or the patient does not respond to repositioning maneuvers, then central disorders can be considered (see Table 3.1).

If the patient presents with acute severe vertigo, then the history and the examination are the key elements. The patient with isolated vertigo has a very low probability of stroke [14], but this may still be a concerning probability. The probability of stroke drops further when isolated vertigo is accompanied by a unidirectional horizontal spontaneous nystagmus [15, 16]. And the probability of stroke drops even further when the patient has isolated vertigo, unidirectional horizontal spontaneous nystagmus, and a corresponding positive head thrust test [15, 16].

If a patient presents with recurrent spontaneous episodes of vertigo, the chance of transient ischemic attack as the cause is low if the symptom lasts for hours, the attacks date back more than a couple of months, and prominent unilateral auditory features are reported. These features are highly suggestive of Meniere's disease. On the other hand, if the attacks are new in onset, brief in duration (minutes rather than hours), and not accompanied by prominent unilateral auditory features, then TIA should be a strong consideration.

Vestibular physical therapy is recommended for patients with acute vestibular neuritis [12]. Regarding medication treatments in patients with vestibular neuritis, a randomized placebo-controlled trial of oral corticosteroids and valacyclovir (2 by 2 factorial design) found that on average patients treated with corticosteroids within 3 days of onset had a superior improvement in vestibular recovery as measured by the surrogate outcome of caloric response at 12 months compared to placebo [13]. Valacyclovir did not demonstrate an average beneficial effect. It is not known if corticosteroids improve functional outcome since functional outcome was not assessed in this trial and many patients with a chronic caloric asymmetry are asymptomatic. If the patient presenting with acute vertigo actually has the Ramsay Hunt syndrome (additional features of vesicles in the external auditory canal and facial palsy, with or without hearing loss) [31], then antiviral treatment is often added since Ramsey Hunt syndrome is of presumed varicella zoster virus (VZV) origin [32]. However, there remains uncertainty because of a lack of adequate trials in Ramsey Hunt syndrome [33, 34], and also because the beneficial effect of antiviral use in the most common VZV disorder (i.e., shingles), is the time to pain recovery and time to skin lesion healing, without evidence of a beneficial long term outcome [32, 35, 36]. Another neuro-otologic cranial nerve neuritis syndrome, "sudden sensorineural hearing loss," also lacks adequate trial data [37] but generally oral corticosteroids are recommended [38]. Interest has increased in the use of intratympanic (IT) corticosteroids injection in sudden sensorineural hearing loss, particularly when used as a "salvage" therapy following failed oral treatment [39, 40], but large and rigorous trials are still necessary to establish the effect.

Regardless of cause, symptoms can be managed with either oral or intravenous medications (Table 3.3). Few randomized controlled trials have been conducted on the symptomatic treatment of acute dizziness. In one study of 74 patients with acute dizziness, the average effect

Table 3.3 Medication options for symptomatic treatment of dizziness

Medication	Dosing
Less sedating	
Dimenhydrinate	50–100 mg PO/IV every 4–6 h
Meclizine	25–50 mg PO every 4–6 h
Scopolamine	0.4 mg PO every 8 h; 1.5 mg topical disc every 3 days
Diphenhydramine	25–50 mg PO/IV every 4–6 h
More sedating	
Prochlorperazine	10 mg PO every 4–6 h
Promethazine	25 mg PO or suppository every 4–6 h
Lorazepam	0.5–2 mg PO/IV every 6–8 h
Diazepam	2–10 mg PO every 6–8 h

PO by mouth, *IV* intravenous.

of 50 mg of intravenous dimenhydrinate was superior to that of 2 mg of intravenous lorazepam [41]. Antinausea medications (e.g., promethazine, prochlorperazine) can be considered when nausea and vomiting are prominent symptoms. One typically begins with less sedating medications. If the effect is not adequate, then more sedating medications are indicated. Patients should be instructed to only use these medicines during the acute phase because use beyond this period is more likely to cause bothersome side effects than any benefit.

Imaging Studies in Emergency Presentations

The use of neuroimaging studies in ED presentations of dizziness has risen dramatically. As noted earlier, in a population of "vertigo-dizziness" ED presentations, more than 25% of patients had a CT scan in 2004 compared with less than 10% of patients in 1995 [2]. In some subgroups, the percent evaluated with a CT scan was nearly 40% [2]. But the sensitivity of CT scans for identifying stroke in the acute setting is a dismal 26% [42], meaning that a negative test does not change the probability of stroke diagnosis in a meaningful way. In addition, CT scans are associated with important downsides, including radiation exposure, increased cost, and increased time in the emergency room. MRI is a much more sensitive test, but is not generally available in the acute setting, takes more time, and has much greater expense. In addition, the sensitivity of MRI is lowest (thus can miss a stroke) when the test is performed within the first 24 h of symptom onset and when the lesion is in the brainstem or cerebellum [16, 42, 43]. A validated clinical decision rule to determine which patients are likely to benefit from neuroimaging could go a long way in optimizing patient outcomes and health-care utilization. But such a rule would need to be supported by policy to have an impact. In the absence of such a rule, clinical judgment must be used when evaluating individual patients. The vertigo patients at highest risk for stroke etiology are those with other focal neurological symptoms or signs (including central patterns of nystagmus), stroke risk factors, acute severe vertigo or imbalance type of presentation, and acute severe vertigo with a negative head thrust test [14–16, 18].

Conclusion

The evaluation of emergency department dizziness patients is facilitated by an organized approach. An accurate assessment of the most likely diagnosis can be made by categorizing the type of presentation and considering the examination findings. The optimal way to "rule out" a central disorder is to "rule in" a specific peripheral vestibular disorder (i.e., vestibular neuritis, BPPV, or Meniere's disease). When the key

clinical features fit with a specific peripheral vestibular disorder, then the likelihood of a serious central disorder is extremely low. CT scans are not a valid discriminator of central versus peripheral vertigo presentations in the emergency department. More research is needed to determine which patients are likely to benefit from neuroimaging in the acute setting.

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Syncope

4

Mark D. Carlson

Abstract

Syncope is defined as transient loss of consciousness due to reduced cerebral blood flow associated with postural collapse and spontaneous recovery. Symptoms and signs that precede syncope may include pallor, diaphoresis, a feeling of warmth, nausea, and visual blurring occasionally proceeding to blindness. Syncope may be benign when it occurs in the absence of heart disease; however, recurrent, unexplained syncope, particularly in an individual with structural heart disease, is associated with a high risk of death (40% mortality within 2 years).

Transiently decreased cerebral blood flow is usually due to one of three general mechanisms: disorders of vascular tone or blood volume, cardiovascular disorders including cardiac arrhythmias, or cerebrovascular disease. Often, the cause of syncope is multifactorial. Disorders of vascular tone or blood volume include neurocardiogenic (vasovagal or vasodepressor) syncope, postural (orthostatic) hypotension, carotid sinus hypersensitivity, and situational syncope (associated with cough, deglutition, micturition, defecation). Cardiovascular disorders that cause syncope include arrhythmias and structural disorders (aortic valvular stenosis, hypertrophic cardiomyopathy, atrial myxoma, pulmonary artery hypertension). Cerebrovascular disease, usually involving the vertebrobasilar arteries is an uncommon cause of syncope.

The treatment of syncope depends on the underlying cause. Lifestyle and behavioral changes, drugs, and permanent pacing have been used to treat neurocardiogenic syncope. Treatment of the cardiovascular causes of syncope (arrhythmias and structural disorders) is often focused on the

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underlying cause (myocardial ischemia, valvular disease, etc.). Regardless of the etiology patients with syncope should be hospitalized with continuous electrocardiographic monitoring when the episode may have resulted from a life-threatening abnormality or if recurrence with significant injury seems likely. Patients who are known to have a normal heart and for whom the history strongly suggests vasovagal or situational syncope may be treated as outpatients if the episodes are neither frequent nor severe.

Keywords
Arrhythmias • Carotid sinus hypersensitivity • Loss of consciousness • Orthostatic hypotension • Syncope

Syncope is defined as transient loss of consciousness due to reduced cerebral blood flow associated with postural collapse and spontaneous recovery. It may occur suddenly, without warning, or be preceded by faintness ("presyncope"). Symptoms and signs that precede syncope may include pallor, diaphoresis, a feeling of warmth, nausea, and visual blurring occasionally proceeding to blindness. These may vary in duration and increase in severity until loss of consciousness occurs or may resolve prior to loss of consciousness if the cerebral ischemia is corrected. It is important, but sometimes challenging, to differentiate syncope from seizure. Syncope may be benign when it occurs as the result of normal cardiovascular reflex effects on heart rate and vascular tone, or serious when it is due to a life-threatening arrhythmia. Syncope may occur as a single event or may be recurrent. Recurrent, unexplained syncope, particularly in an individual with structural heart disease, is associated with a high risk of death (40% mortality within 2 years).

Causes

Transiently decreased cerebral blood flow is usually due to one of three general mechanisms: disorders of vascular tone or blood volume, cardiovascular disorders including cardiac arrhythmias, or cerebrovascular disease. Often, the cause of syncope is multifactorial.

Disorders of Vascular Tone or Blood Volume

Disorders of autonomic control of the heart and circulation share common pathophysiologic mechanisms: a cardioinhibitory component (e.g., bradycardia due to increased vagal activity), a vasodepressor component (e.g., inappropriate vasodilatation due to sympathetic withdrawal), or both.

Neurocardiogenic (Vasovagal and Vasodepressor) Syncope

The term *neurocardiogenic* encompasses both vasovagal and vasodepressor forms of syncope. Vasovagal syncope is associated with both sympathetic withdrawal (vasodilatation) and increased parasympathetic activity (bradycardia), whereas vasodepressor syncope is associated with sympathetic withdrawal alone. These types of syncope are and account for about one-half of syncopal episodes including the common faint that may occur in the absence of disease. Neurocardiogenic syncope is frequently recurrent and is commonly precipitated by a hot or crowded environment, extreme fatigue, severe pain, hunger, alcohol ingestion, prolonged standing, and an emotional or stressful event. The syndrome usually occurs when individuals are in the standing position and rarely occurs when supine. Although often preceded by weakness, nausea, diaphoresis,

light-headedness, or blurred vision, in some individuals, syncope may occur abruptly, without warning.

The unconscious patient usually lies motionless with skeletal muscles relaxed, but clonic jerks of the limbs and face may occur. In contrast to a seizure, individuals rarely lose sphincter control. The pulse and blood pressure may be undetectable, and breathing is almost imperceptible. The duration of unconsciousness is rarely longer than a few minutes if the conditions that provoked the episode are reversed. When placed supine, most individuals recover rapidly. Although commonly benign, neurocardiogenic syncope can be associated with prolonged asystole and hypotension, resulting in injury.

The syncope often occurs in this setting of increased peripheral sympathetic activity and venous pooling. Under these conditions, vigorous myocardial contraction of a relatively empty left ventricle activates myocardial mechanoreceptors and vagal afferent nerve fibers that inhibit sympathetic activity and increase parasympathetic activity. The resultant vasodilatation and bradycardia induce hypotension and syncope.

Although this reflex is generally thought to be responsible for neurocardiogenic syncope, other reflexes may also be operative. Patients with transplanted (denervated) hearts have experienced cardiovascular responses identical to those present during neurocardiogenic syncope, which, unless the heart has become reinnervated, should not be possible if the response depends solely on the reflex mechanisms described above. Moreover, neurocardiogenic syncope often occurs in response to stimuli (fear, emotional stress, or pain) that may not be associated with venous pooling in the lower extremities, which suggests a cortical component to the reflex. Thus, a variety of afferent and efferent responses may cause neurocardiogenic syncope.

The central nervous system (CNS) mechanisms responsible for neurocardiogenic syncope are uncertain, but a sudden surge in central serotonin levels may contribute to the sympathetic withdrawal. Endogenous opiates (endorphins) and adenosine are also putative participants in the pathogenesis.

Postural (Orthostatic) Hypotension

This occurs in patients who have chronic or episodic instability of vasomotor reflexes. Systemic arterial blood pressure falls on assumption of upright posture due to loss of vasoconstriction reflexes in lower extremity resistance and capacitance vessels. Although the episode differs little from vasodepressor syncope, the effect of posture is critical. Sudden rising from a recumbent position or standing quickly may precipitate episodes. *Orthostatic hypotension may be the cause in up to 30% of elderly individuals who experience syncope; antihypertensive or antidepressant drugs often contribute to syncope in these patients.* Postural syncope may occur in otherwise normal persons with defective postural reflexes. Patients with *idiopathic postural hypotension* may be identified by a characteristic response to upright tilt. Initially, the blood pressure diminishes slightly before stabilizing at a lower level. Thereafter, compensatory reflexes fail and arterial pressure falls precipitously. Orthostatic hypotension, often accompanied by disturbances in sweating, impotence, and sphincter difficulties, also occurs in patients with autonomic nervous system disorders. The most common causes of neurogenic orthostatic hypotension are chronic diseases of the peripheral nervous system that involve postganglionic unmyelinated fibers (e.g., diabetic, nutritional, and amyloid polyneuropathy). Much less common are the multiple system atrophies; CNS disorders in which orthostatic hypotension is associated with (1) parkinsonism but the autonomic dysfunction predominates (Shy-Drager syndrome), (2) olivopontocerebellar atrophy when progressive cerebellar degeneration is a predominant feature, or (3) striatonigral degeneration when parkinsonian features, such as bradykinesia and rigidity, predominate. A rare, acute postganglionic dysautonomia may represent a variant of Guillain–Barre´ syndrome. There are several additional causes of postural syncope: (1) after physical deconditioning (such as after prolonged illness with recumbency, particularly in elderly individuals with reduced muscle tone) or

after prolonged weightlessness, as in space flight; (2) after sympathectomy that has abolished vasopressor reflexes; and (3) in patients receiving antihypertensive or vasodilator drugs and those who are hypovolemic because of diuretics, excessive sweating, diarrhea, vomiting, hemorrhage, or adrenal insufficiency.

Carotid Sinus Hypersensitivity

Syncope due to carotid sinus hypersensitivity is precipitated by pressure on the carotid sinus baroreceptors, located just cephalad to the bifurcation of the common carotid artery. Carotid sinus hypersensitivity occurs predominantly in men over 50 years old, typically in the setting of shaving, a tight collar, or turning the head to one side. Activation of carotid sinus baroreceptors gives rise to impulses carried via the nerve of Hering, a branch of the glossopharyngeal nerve, to the medulla oblongata. These afferent impulses activate efferent sympathetic nerve fibers to the heart and blood vessels, cardiac vagal efferent nerve fibers, or both. In patients with carotid sinus hypersensitivity, these responses may cause sinus arrest or atrioventricular (AV) block (a cardioinhibitory response), vasodilatation (a vasodepressor response), or both (a mixed response). The mechanisms responsible for the syndrome are not clear and validated diagnostic criteria do not exist.

Situational Syncope

A variety of activities, including cough, deglutition, micturition, and defecation, are associated with syncope in susceptible individuals. These syndromes are caused, at least in part, by abnormal autonomic control and may involve a cardioinhibitory response, a vasodepressor response, or both. Cough, micturition, and defecation are associated with maneuvers (such as Valsalva and straining) that increase intrathoracic pressure and increase intracranial pressure both of which can contribute to decreased cerebral blood flow. Cough syncope typically occurs during or immediately after prolonged coughing fits in men with chronic bronchitis or chronic obstructive lung disease. Micturition syncope occurs predominantly in middle-aged and older men, particularly those with prostatic hypertrophy and obstruction of the bladder neck; loss of consciousness usually occurs at night during or immediately after voiding. Deglutition syncope and defecation syncope occur in men and women. Deglutition syncope may be associated with esophageal disorders, particularly esophageal spasm. In some individuals, particular foods and carbonated or cold beverages initiate episodes by activating esophageal sensory receptors that trigger reflex sinus bradycardia or AV block. Defecation syncope may occur secondary to a Valsalva maneuver in older individuals with constipation.

Glossopharyngeal Neuralgia

Syncope due to glossopharyngeal neuralgia is preceded by pain in the oropharynx, tonsillar fossa, or tongue. Loss of consciousness is usually associated with asystole rather than vasodilatation. The mechanism is thought to involve activation of afferent impulses in the glossopharyngeal nerve that terminate in the nucleus solitarius of the medulla, and via collaterals activate the dorsal motor nucleus of the vagus nerve.

Cardiovascular Disorders

Cardiac syncope results from a sudden reduction in cardiac output, caused most commonly by a cardiac arrhythmia but also by structural abnormalities that obstruct blood flow.

Arrhythmias

In normal individuals, heart rates between 30 and 180 beats/min do not reduce cerebral blood flow, especially when the person is supine. As the heart rate decreases, ventricular filling time and stroke volume increase to maintain normal

cardiac output. At rates less than 30 beats/min, stroke volume can no longer increase to compensate adequately for the decreased heart rate. At rates greater than 180 beats/min, ventricular filling time is often insufficient to maintain adequate stroke volume. Upright posture; cerebrovascular disease; anemia; loss of atrioventricular synchrony; and coronary, myocardial, or valvular disease all reduce the tolerance to alterations in rate. Bradyarrhythmias may occur as a result of an abnormality of impulse generation (e.g., sinoatrial arrest) or impulse conduction (e.g., AV block). Either may cause syncope if the escape pacemaker rate is insufficient to maintain cardiac output. Syncope due to bradyarrhythmias may occur abruptly, without preceding symptoms, and recur several times daily. Patients with *sick sinus syndrome* may have sinus pauses (>3 s), and those with syncope due to high degree AV block (*Stokes-Adams-Morgagni syndrome*) may have evidence of conduction system disease (e.g., prolonged PR interval, bundle branch block). However, the arrhythmia is often transitory, and the surface electrocardiogram or the continuous electrocardiographic monitor placed later may not reveal the abnormality. The *bradycardia–tachycardia syndrome* is a common form of sinus node dysfunction in which syncope generally occurs as a result of marked sinus pauses, some following termination of an atrial tachyarrhythmia. Drugs are a common cause for bradyarrhythmias, particularly in patients with underlying structural heart disease. Digoxin, adrenergic receptor antagonists, calcium channel blockers, and many antiarrhythmic drugs may suppress sinoatrial node impulse generation or slow AV nodal conduction.

Syncope due to a *tachyarrhythmia* is usually preceded by palpitation or light-headedness but may occur abruptly without warning. *Supraventricular tachyarrhythmias* are unlikely to cause syncope in individuals with structurally normal hearts but may do so if they occur in patients with (1) heart disease that also compromises cardiac output, (2) cerebrovascular disease, (3) a disorder of vascular tone or blood volume, or (4) a rapid ventricular rate. These tachycardias result most commonly from paroxysmal atrial flutter, atrial fibrillation, or reentry involving the AV node or accessory pathways that bypass part or all of the AV conduction system. Patients with the *Wolff–Parkinson–White syndrome* may experience syncope when a very rapid ventricular rate occurs due to reentry across an accessory AV connection. In patients with structural heart disease, ventricular tachycardia is a common cause of syncope, particularly in patients with a prior myocardial infarction. Patients with aortic valvular stenosis and hypertrophic obstructive cardiomyopathy are also at risk for ventricular tachycardia. Individuals with abnormalities of ventricular repolarization (prolongation of the QT interval) are at risk to develop polymorphic ventricular tachycardia (*torsades de pointes*). Those with the inherited form of this syndrome often have a family history of sudden death in young individuals. Genetic markers can identify some patients with familial long QT syndrome, but the clinical utility of these markers remains unproven. Drugs (i.e., certain antiarrhythmics and erythromycin) and electrolyte disorders (i.e., hypokalemia, hypocalcemia, hypomagnesemia) can prolong the QT interval and predispose to torsades de pointes. Antiarrhythmic medications may precipitate ventricular tachycardia, particularly in patients with structural heart disease.

Structural Disorders

In addition to arrhythmias, syncope may also occur with a variety of structural cardiovascular disorders. Episodes are usually precipitated when the cardiac output cannot increase to compensate adequately for peripheral vasodilatation. Peripheral vasodilatation may be appropriate, such as following exercise, or may occur due to inappropriate activation of left ventricular mechanoreceptor reflexes, as occurs in aortic outflow tract obstruction (aortic valvular stenosis or hypertrophic obstructive cardiomyopathy). Obstruction to forward flow is the most common reason that cardiac output cannot increase. Syncope occurs in up to 10% of patients with massive pulmonary embolism and may occur

with exertion in patients with severe primary pulmonary hypertension. The cause is an inability of the right ventricle to provide appropriate cardiac output in the presence of obstruction or increased pulmonary vascular resistance. Loss of consciousness is usually accompanied by other symptoms such as chest pain and dyspnea. Atrial myxoma, a prosthetic valve thrombus, and, rarely, mitral stenosis may impair left ventricular filling, decrease cardiac output, and cause syncope. Pericardial tamponade is a rare cause of syncope.

Cerebrovascular Disease

Cerebrovascular disease alone rarely causes syncope but may lower the threshold for syncope in a patient with another cause. In such cases, the vertebrobasilar arteries, which supply brainstem structures responsible for maintaining consciousness, are usually involved. An exception is the unusual patient with tight bilateral carotid stenoses and recurrent syncope, often precipitated by standing or walking. Most patients who experience light-headedness or syncope due to cerebrovascular disease also have symptoms of focal neurologic ischemia, such as arm or leg weakness, diplopia, ataxia, dysarthria, or sensory disturbances. Basilar artery migraine is a rare disorder that can cause syncope in adolescents.

Differential Diagnosis

Anxiety Attacks and the Hyperventilation Syndrome

Anxiety, such as occurs in panic attacks, is frequently interpreted as a feeling of faintness or dizziness resembling presyncope. The symptoms are not accompanied by facial pallor and are not relieved by assuming a recumbent position. The diagnosis is made on the basis of the associated symptoms, such as a feeling of impending doom, air hunger, palpitations, and tingling of the fingers and perioral region. Attacks can often be reproduced by hyperventilation, resulting in hypocapnia, alkalosis, increased cerebrovascular resistance, and decreased cerebral blood flow. The release of epinephrine also contributes to the symptoms.

Seizures

Unlike syncope, a seizure may be heralded by an aura, which is caused by a focal seizure discharge and hence has localizing significance. The aura is usually followed by a rapid return to normal or by a loss of consciousness. Injury from falling is frequent in a seizure and rare in syncope, since only in generalized seizures are protective reflexes abolished instantaneously. Sustained tonic-clonic movements are characteristic of convulsive seizures but brief clonic, or tonic-clonic, seizure-like activity can accompany fainting episodes. The period of unconsciousness tends to be longer in seizures than in syncope. Urinary incontinence is frequent in seizures and rare in syncope. The return of consciousness is prompt in syncope, slow after a seizure. Mental confusion, headache, and drowsiness are common sequelae of seizures, whereas physical weakness with a clear sensorium characterizes the postsyncopal state. Repeated spells of unconsciousness in a young person at a rate of several per day or month suggest epilepsy rather than syncope.

Hypoglycemia

Severe hypoglycemia is usually due to a serious disease such as a tumor of the islets of Langerhans; advanced adrenal, pituitary, or hepatic disease; or to excessive administration of insulin.

Acute Hemorrhage

Hemorrhage, usually within the gastrointestinal tract, is an occasional cause of syncope. In the absence of pain and hematemesis, the cause of the weakness, faintness, or even unconsciousness may remain obscure until the passage of a black stool.

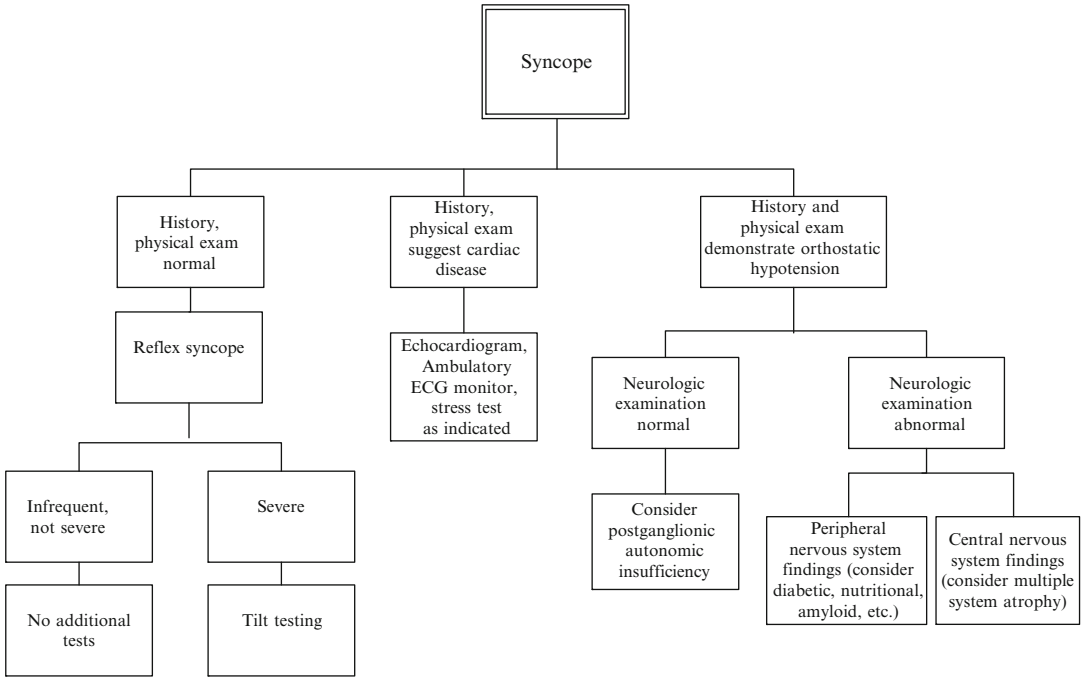

Fig. 4.1 Approach to diagnosing the cause of syncope

Hysterical Fainting

The attack is usually unattended by an outward display of anxiety. Lack of change in pulse and blood pressure or color of the skin and mucous membranes distinguishes it from the vasodepressor faint.

Approach to the Patient

The diagnosis of syncope is often challenging. The cause may only be apparent at the time of the event, leaving few, if any, clues when the patient is seen later by the physician. The physician should think first of those causes that constitute a therapeutic emergency. Among them are massive internal hemorrhage or myocardial infarction, which may be painless, and cardiac arrhythmias. In elderly persons, a sudden faint, without obvious cause, should arouse the suspicion of complete heart block or a tachyarrhythmia, even though all findings are negative when the patient is seen. Figure 4.1 depicts an algorithmic approach to syncope. A careful history is the most important diagnostic tool, both to suggest the correct cause and to exclude important potential causes. The nature of the events and their time course prior to, during, and after an episode of syncope often provide valuable etiologic clues. Loss of consciousness in particular situations, such as during venipuncture, micturition, or with volume depletion, suggests an abnormality of vascular tone. The position of the patient at the time of the syncopal episode is important; syncope in the supine position is unlikely to be vasovagal and suggests an arrhythmia or a seizure. Syncope due to carotid sinus syndrome may occur when the individual is wearing a shirt with a tight collar, turning the head (turning to look while driving in reverse), or manipulating the neck (as in shaving). The patient's medications must be noted, including nonprescription drugs or health store supplements, with particular attention to recent changes. Heart rate and blood pressure should be evaluated in the supine,

sitting, and standing positions. In patients with unexplained recurrent syncope, an attempt to reproduce an attack may assist in diagnosis.

Anxiety attacks induced by hyperventilation can be reproduced readily by having the patient breathe rapidly and deeply for 2–3 min. Cough syncope may be reproduced by inducing the Valsalva maneuver. Carotid sinus massage should generally be avoided, even in patients with suspected carotid sinus hypersensitivity; it can cause a transient ischemic attack (TIA) or stroke in individuals with carotid atheromas.

Diagnostic Tests

The history and physical examination guide the choice of diagnostic tests. Although unlikely to provide a definitive diagnosis, a surface 12-lead electrocardiogram may provide clues to the cause of syncope *and should be performed in almost all patients*. The presence of conduction abnormalities (PR prolongation and bundle branch block) suggests a bradyarrhythmia, whereas pathologic Q waves or prolongation of the QT interval suggests a ventricular tachyarrhythmia. Inpatients should undergo continuous electrocardiographic monitoring; outpatients should wear a Holter monitor for 24–48 h. Newer monitors are able to monitor surface ECG leads for up to 10 days. Symptoms should be correlated with the occurrence of arrhythmias. Cardiac event monitors may be useful in patients with infrequent symptoms, particularly in patients with presyncope.

Measurements of serum electrolytes, glucose, and the hematocrit are usually indicated and cardiac enzymes should be evaluated if myocardial ischemia is suspected. Blood and urine toxicology screens may reveal the presence of alcohol or other drugs. In patients with possible adrenocortical insufficiency, plasma aldosterone and mineralocorticoid levels should be obtained.

Invasive cardiac electrophysiologic testing provides diagnostic and prognostic information regarding sinus node function, AV conduction, and supraventricular and ventricular arrhythmias. Continuous electrocardiographic monitoring is usually more effective for diagnosing sinus node disease. However, invasive electrophysiologic testing is useful for detecting His-Purkinje disease, and in patients who have experienced a myocardial infarction, ventricular arrhythmias that may be responsible for syncope.

Upright tilt table testing is indicated for recurrent syncope or a single syncopal episode that caused or could cause injury were it to recur, particularly if the patient is likely to be in a "high-risk" setting (pilot, commercial vehicle driver, etc.). In susceptible patients, upright tilt at an angle between 60° and 80° for 30–60 min induces a vasovagal episode particularly when accompanied with administration of drugs that cause venous pooling or increase adrenergic stimulation (isoproterenol, nitroglycerin, edrophonium, or adenosine). The sensitivity and specificity of tilt table testing are difficult to ascertain because of the lack of validated criteria. Moreover, the reflexes responsible for vasovagal syncope can be elicited in most, if not all, individuals given the appropriate stimulus. The reported accuracy of the test ranges from 30% to 80%, depending on the population studied and the techniques used. Whereas the reproducibility of a negative test is 85–100%, the reproducibility of a positive tilt table test is only between 62% and 88%. A variety of other tests may be useful to determine the presence of structural heart disease that may cause syncope.

The echocardiogram with Doppler examination detects valvular, myocardial, and pericardial abnormalities. The echocardiogram is the "gold standard" for the diagnosis of hypertrophic cardiomyopathy and atrial myxoma. Cardiac cine magnetic resonance (MR) imaging provides an alternative noninvasive modality that may be useful for patients in whom diagnostic-quality echocardiographic images cannot be obtained. This test is also indicated for patients suspected of having arrhythmogenic right ventricular dysplasia or right ventricular outflow tract ventricular tachycardia. Both are associated with right ventricular structural abnormalities that are better visualized on MR imaging than by echocardiogram. Exercise testing may detect ischemia or exercise-induced arrhythmias. In some patients, cardiac catheterization may be necessary to

diagnose the presence or severity of coronary artery disease or valvular abnormalities. Ultrafast computed tomographic scan, ventilation–perfusion scan, or pulmonary angiography is indicated in patients in whom syncope may be due to pulmonary embolus.

In possible cases of cerebrovascular syncope, neuroimaging tests may be indicated, including Doppler ultrasound studies of the carotid and vertebrobasilar systems, MR imaging, MR angiography, and CT angiography of the cerebral vasculature. Electroencephalography is indicated if seizures are suspected.

Treatment

The treatment of syncope depends on the underlying cause. With respect to the disorders of autonomic control, certain precautions should be taken regardless of the specific cause of syncope. Patients with frequent episodes, or those who have experienced syncope without warning symptoms, should avoid situations in which sudden loss of consciousness might result in injury (e.g., climbing ladders, swimming alone, operating heavy machinery, driving, etc.). At the onset of symptoms, patients should take steps to avoid injury should they lose consciousness, lowering their head and preferably lying down. Lowering the head by bending at the waist should be avoided because it may further compromise venous return to the heart. Family members or other close contacts should be informed of the problem in order to ensure appropriate therapy and prevent delivery of inappropriate therapy (chest compressions associated with cardiopulmonary resuscitation) that may inflict trauma. Patients who have lost consciousness should be placed in a position that maximizes cerebral blood flow, offers protection from trauma, and secures the airway. Whenever possible, the patient should be placed supine with the head turned to the side to prevent aspiration and the tongue from blocking the airway. Assessment of the pulse and direct cardiac auscultation may assist in determining if the episode is associated with a bradyarrhythmia or tachyarrhythmia. Clothing that fits tightly around the neck or waist should be loosened. Patients should not be given anything by mouth or be permitted to rise until full consciousness has returned.

Patients with vasovagal syncope should be instructed to avoid situations or stimuli that have caused them to lose consciousness and to assume a recumbent position when premonitory symptoms occur. This alone may be sufficient therapy for patients with infrequent and relatively benign episodes of vasovagal syncope, particularly when episodes occur in response to a specific stimulus. Tilt training (standing and leaning against a wall for progressively longer periods each day) has been used with limited success, particularly for those patients who have profound orthostatic intolerance. Episodes associated with intravascular volume depletion may be prevented by salt and fluid loading prior to provocative events.

Prescription drug therapy may be necessary when vasovagal syncope is resistant to these measures, when episodes occur frequently, or when syncope is associated with a significant risk for injury. Adrenergic receptor antagonists (metoprolol, 25–50 mg bid; atenolol, 25–50 mg qd; or nadolol, 10–20 mg bid; all starting doses), the most widely used agents, mitigate the increase in myocardial contractility that stimulates left ventricular mechanoreceptors and also block central serotonin receptors. Serotonin reuptake inhibitors (paroxetine, 20–40 mg qd; or sertraline, 25–50 mg qd), appear to be effective for some patients. Bupropion SR (150 mg qd), another antidepressant, has also been used with success. Adrenergic receptor antagonists and serotonin reuptake inhibitors are well tolerated and are often used as first-line agents for younger patients. Hydrofludrocortisone (0.1–0.2 mg qd), a mineralocorticoid, promotes sodium retention, volume expansion, and peripheral vasoconstriction by increasing receptor sensitivity to endogenous catecholamines. Hydrofludrocortisone is useful for patients with intravascular volume depletion and those who also have postural hypotension. Proamatine, an alpha agonist, has been used as a first-line agent for some patients. In a randomized controlled trial, proamatine was more effective than placebo in preventing syncope

during an upright tilt test. However, in some patients, proamatine and hydrofludrocortisone may increase resting supine systemic blood pressure, a property that may be problematic for those with hypertension.

Disopyramide (150 mg bid), a vagolytic antiarrhythmic drug with negative inotropic properties, and another vagolytic, transdermal scopolamine, have been used to treat vasovagal syncope, as have theophylline and ephedrine. Side effects associated with these drugs have limited their use for this indication. Disopyramide is a type 1A antiarrhythmic drug and should be used with great caution, if at all, in patients who are at risk for ventricular arrhythmias. Although several clinical trials have suggested that pharmacologic therapy for vasovagal syncope is effective, long-term prospective randomized controlled trials have yet to be completed.

Permanent dual-chamber cardiac pacing is effective for patients with frequent episodes of vasovagal syncope and is indicated for those with prolonged asystole associated with vasovagal episodes. Patients in whom vasodilatation contributes to loss of consciousness may also experience symptomatic benefit from permanent pacing. Pacemakers that can be programmed to transiently pace at a high rate (90–100 beats/min) after a profound drop in the patient's intrinsic heart rate are most effective. Patients with orthostatic hypotension should be instructed to rise slowly and systematically (supine to seated, seated to standing) from the bed or a chair. Movement of the legs prior to rising facilitates venous return from the lower extremities. Whenever possible, medications that aggravate the problem (vasodilators, diuretics, etc.) should be discontinued. Elevation of the head of the bed [20–30 cm (8–12 in)] and use of compression stockings may help. Additional therapeutic modalities include an antigravity or g suit or compression stockings to prevent lower limb blood pooling, salt loading, and a variety of pharmacologic agents including sympathomimetic amines, monoamine oxidase inhibitors, beta blockers, and levodopa.

Glossopharyngeal neuralgia is treated with carbamazepine, which is effective for the syncope as well as for the pain. Patients with carotid sinus syndrome should be instructed to avoid clothing and situations that stimulate carotid sinus baroreceptors. When looking to the side, they should turn their entire body, rather than just their head. Those with intractable syncope due to the cardioinhibitory response to carotid sinus stimulation should undergo permanent pacemaker implantation.

Treatment of the cardiovascular causes of syncope (arrhythmias and structural disorders) is often focused on the underlying cause (myocardial ischemia, valvular disease, etc.). Patients with bradyarrhythmias may benefit from permanent pacing. Those with certain supraventricular arrhythmias may benefit from catheter ablation. An implantable cardioverter defibrillator is indicated for patients with or at high risk for life-threatening ventricular arrhythmias. Surgical replacement is indicated for patients with critical aortic valvular stenosis.

Regardless of the etiology, patients with syncope should be hospitalized with continuous electrocardiographic monitoring when the episode may have resulted from a life-threatening abnormality or if recurrence with significant injury seems likely. Patients who are known to have a normal heart and for whom the history strongly suggests vasovagal or situational syncope may be treated as outpatients if the episodes are neither frequent nor severe.

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Acute Visual Loss

5

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Abstract

Visual loss is a common symptom in neurologic emergencies. Although ocular causes of visual loss are usually identified by eye care specialists, many patients appear in an emergency department or a neurologist's office when the ocular examination is normal or when it suggests a neurologic disorder. Indeed, many causes of monocular or binocular acute visual loss may reveal or precede a neurologic process. In this situation, a quick and simple clinical examination done at bedside in the emergency department allows the neurologist to localize the lesion and determine whether an urgent neurologic workup or further ophthalmologic consultation is necessary.

Keywords

Central retinal artery occlusion • Funduscopic examination • Optic neuropathy • Retinal emboli • Visual field • Visual loss

Acute vision changes typically precipitate emergency consultation. Although ocular causes are usually identified by eye care specialists, many patients appear in an emergency department or a neurologist's office when the ocular examination is normal or when it suggests a neurologic disorder. Indeed, many causes of monocular or binocular acute visual loss may reveal or precede a neurologic process. In this situation, a quick and simple clinical examination done at bedside in the emergency department allows the neurologist to localize the lesion and determine whether an

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urgent neurologic workup or further ophthalmologic consultation is necessary [1, 2].

The Neuro-Ophthalmologic Examination in the Emergency Department

Evaluation of visual function, examination of the pupils and extraocular movements, and ocular funduscopic examination are all part of the routine neurologic examination. They are particularly important when the patient has visual symptoms, or when the neurologic disorder involves the intracranial visual pathways or is classically associated with neuro-ophthalmic manifestations or complications. Often, a detailed neuro-ophthalmic examination provides helpful clues regarding the mechanism of neurologic symptoms and signs and guides the neurologist when making acute management decision in the patient with visual complaints. The only tools needed are a near visual acuity card (but a magazine from the waiting room can be sufficient), a bright red object, a bright light for external and pupil examinations, and a direct ophthalmoscope.

Visual Acuity

Visual acuity is easily measured in cooperative patients in the emergency department or in the neurologist's office. Each eye must be tested separately and patients should wear their corrective lenses (glasses or contact lens) during the examination. A near card (or even your name tag or a magazine) is good enough to test visual acuity. Patients over the age of 50 must wear their reading glasses (or a +3 lens must be used). If visual acuity is improved when the patient looks through small holes made on a piece of cardboard (so-called pinhole), the problem is refractive or ocular, and not neurologic in origin. This pinhole is also useful to estimate distance visual acuity when patients do not have their glasses. If the vision loss is so profound that the patient cannot see anything on the near card, vision is measured as "count fingers," "hand motion," "light perception," or "no light perception."

Color Vision

Color vision testing is important to localize the lesion to the optic nerve or to detect subtle visual changes when visual acuity is normal. Altered color vision can be the only early sign of an optic neuropathy. A simple way to test it at bedside in patients complaining of unilateral vision loss is to present a bright red object to each eye and to ask the patient to estimate the amount of "redness" in each eye [1]. Unilateral optic neuropathies will produce red desaturation (dimmer or darker red) in the affected eye. A more formal and quantitative way to test color vision is with Ishihara or Hardy Rand Ritter pseudoisochromatic color plates.

Visual Fields

Visual fields are usually assessed in the emergency department by confrontation methods, and can be of great value in helping localize the lesion. As for visual acuity, visual fields are tested one eye at a time, with special attention directed to the horizontal and vertical axes of the visual field. One eye is occluded and the patient is instructed to count fingers presented within the central 30° by the physician while the patient looks at the examiner's opposite eye or nose, and maintains fixation. The patient must perform the task equally well in all four quadrants. An asymmetry along the horizontal axis in one eye is most suggestive of optic nerve disease, whereas an abrupt change across the vertical meridian signals visual loss of intracranial origin. For more peripheral visual field testing, finger movements may be used because these parts of the visual field are more sensitive to motion than shape. If the visual field defect is within the central 10° and too small to be detected by confrontation testing, the Amsler grid is useful to test the central visual field at bedside.

Formal visual field testing, such as Goldmann or automated perimetry, provides a more standardized examination, will reveal more subtle abnormalities, and can quantify the defects in order to follow disease progression. These tests are easily performed in an ophthalmologist's office once the patient is stable and able to cooperate.

Examination of the Pupils

Pupillary examination in the dark and in the light provides valuable information about the afferent and efferent visual pathways. Because both pupillary reactions to light and pupillary dilation in the dark are examined, it is essential to turn the lights off to ensure that the level of light is low enough (which may be challenging in the emergency department or in an ICU).

The search for a relative afferent pupillary defect (RAPD) is of great importance, particularly when visual loss is unilateral or asymmetric. Indeed, the presence of an RAPD in the setting of a normal-appearing retina is diagnostic of a unilateral or asymmetric optic neuropathy. Exceptions include severe retinal diseases, such as retinal vascular occlusions, and large retinal detachments, which are easily seen on funduscopic examination. Corneal abnormalities, cataracts, and macular disorders do *not* cause a RAPD.

Unless the patient has a history of an ocular disorder (such as surgery or uveitis), anisocoria reflects an efferent problem which may be either a dilation problem (the smaller pupil does not dilate well) or a constriction problem (the larger pupil does not constrict well). Poor dilation reflects a lesion involving the sympathetic pathways, such as from Horner syndrome, whereas poor constriction reflects a lesion involving the parasympathetic pathways such as a third nerve palsy, tonic pupil, or pharmacologic mydriasis. Horner syndrome with acute visual loss points to the internal carotid artery, and may be the first sign of a carotid dissection, whereas an acute third nerve palsy with visual loss is highly suggestive of pituitary apoplexy with chiasmal and cavernous sinus compression.

Eye Movements

Diplopia and ocular motility are discussed in detail in Chap. 6. Some patients describe diplopia as "visual loss or blurriness" that resolves with covering either eye. True monocular or binocular visual loss in association with abnormal eye movements should help localize the lesion (e.g., to the orbital apex or to the sellar region).

Ocular Examination and Funduscopic Examination

The ocular examination itself is usually the domain of the ophthalmologist, but careful penlight examination at bedside may reveal obvious abnormalities of the anterior portion of the eye (such as the cornea or lens) that could be the cause of decreased vision or that could obstruct an adequate view of the fundus [3]. Abnormalities of the ocular media sufficient to cause severe visual loss usually result in a poor view of the ocular fundus: "*If you can't see in, the patient can't see out*." When media opacity is suspected, the visual acuity should be tested without and with pinhole. Redness of the conjunctiva usually indicates a problem involving the anterior segment of the eye. Any ocular redness or pain associated with vision loss is usually an ophthalmic emergency and should prompt an immediate ophthalmologic consultation. Corneal ulcerations, uveitis, and angle-closure glaucoma present with acute painful visual loss (Fig. 5.1).

Examination of the ocular fundus is essential in all patients complaining of visual loss. Pharmacologic dilation of the pupils with short-acting drops, such as a parasympathetic antagonist (tropicamide) and a sympathetic agonist (phenylephrine), allows the best and easiest view of the optic nerve, macula, and blood vessels. Phenylephrine should be avoided in patients with severe systemic hypertension or malignant

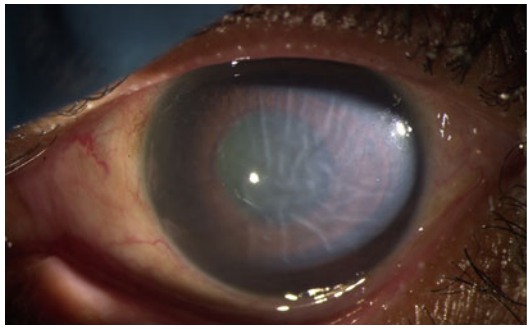

Fig. 5.1 Acute angle-closure glaucoma in the left eye with acute painful vision loss. The eye is red and the cornea is cloudy. The pupil is dilated and not reactive to light. On palpation, the eye feels hard

hypertension. Pupillary dilation occurs within 30 min and usually resolves within 6 h. Both pupils should be dilated at the same time, and time of instillation and agent used should be noted in the chart in the emergency department. Identification of optic nerve head edema, optic nerve head pallor, retinal whitening, retinal hemorrhages, attenuation of the arteries, dilation of the veins, retinal emboli, or vitreous hemorrhages is extremely useful in neurologic emergencies and allows the neurologist to manage these patients appropriately before even requesting an ophthalmic consultation. Optic nerve pallor takes about 6 weeks to develop regardless of the mechanism of optic nerve injury; therefore, the finding of optic nerve pallor in a patient complaining of acute visual loss suggests that the visual loss is related to an underlying long-standing process. For example, a patient with a previously undiagnosed pituitary mass may notice the visual loss only at the time of pituitary apoplexy, or some patients with long-standing optic atrophy and visual loss may erroneously blame the visual loss on a recent trauma.

Where Is the Lesion?

In most cases, vision loss results from ocular disorders, and an ophthalmologist should be consulted first in the emergency department when a patient presents with acute visual changes. Ocular redness, eye pain, or an abnormal fundus help localize the lesion to the eye and often reveal ocular emergencies. More rarely, however, the ocular examination does not explain the visual loss and an optic neuropathy or an intracranial process is suspected; sometimes, the ophthalmologist or emergency department physician identifies a sign suggestive of a neurologic disorder, such as optic nerve head edema, bitemporal or homonymous visual field changes, an efferent pupillary disorder, or abnormal extraocular movements. A neurologic consultation should also be requested when the patient is diagnosed with acute retinal ischemia (transient or permanent) or retinal emboli, which may precede a cerebral infarction and warrant urgent neurovascular evaluation.

Ocular Causes of Acute Vision Loss: What the Neurologist Should Know

Painful Red Eye with Vision Loss

Acute vision loss with eye pain, photophobia, tearing, and eye redness suggests an ocular disease involving the anterior segment of the eye [3]. These disorders are mostly unilateral. Trauma, corneal infections, anterior uveitis, and acute angle-closure glaucoma are classic causes of acute visual loss with pain, which should always prompt an immediate examination by an ophthalmologist [4–8].

Patients with corneal ulcerations or trauma are often unable to open their eye because of reflex blepharospasm. Angle-closure glaucoma is suspected when the vision loss is preceded by severe eye pain and headaches and often associated with nausea. The eye becomes red rapidly and patients typically complain of seeing halos around lights in addition to blurry vision. The cornea is cloudy and the pupil is dilated, not reactive to light (Fig. 5.1). Palpation of both eyes allows the neurologist to realize that the affected eye feels harder than the normal eye. Uveitis can only be diagnosed with slit lamp examination: most patients complain of photophobia, floaters, and mild pain, and the eye may be moderately or very red.

Vision Loss with Abnormal Retina

A few neurologic emergencies may present with acute visual loss and retinal changes. Intravitreal and preretinal hemorrhages cause acute visual loss without pain. The anterior segment of the eye looks normal, there is no RAPD, and the view of the fundus is difficult; when looking at the eye with an ophthalmoscope a few inches away, the examiner sees a dull or dark reflex in the center of the cornea indicating the absence of the normal red reflex. Vitreous hemorrhage is common in diabetic patients, and it may also occur in patients with acute intracranial hypertension, particularly resulting from subarachnoid hemorrhage (so-called Terson syndrome) (Fig. 5.2) [9].

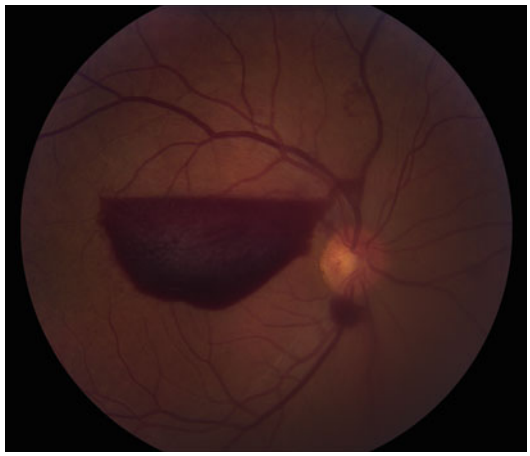

Fig. 5.2 Terson syndrome in the right eye of a patient with subarachnoid hemorrhage. There is a large preretinal hemorrhage as well as two small peripapillary hemorrhages

Retinal diseases such as central retinal artery occlusion (CRAO) (Fig. 5.3), and large retinal detachments, can produce acute painless monocular visual loss with an RAPD. The RAPD is present because the retinal ganglion cells (whose axonal projections become the optic nerve) in the inner layers of the retina are affected by these processes. This is why a dilated funduscopic examination is necessary before localizing the lesion to the optic nerve in all patients with vision loss and an RAPD. CRAO produces acute, painless, severe, and permanent monocular visual loss resulting from acute inner retinal ischemia. The inner retina, which includes the ganglion cells, is infarcted and there is a dense RAPD. Funduscopic examination shows marked attenuation of the retinal arteries, sometimes occluded by emboli, and whitening of the ischemic inner retina with sparing of the outer retina in the foveal region supplied by the intact choroidal circulation, creating the classic "cherry-red spot" (Fig. 5.3) [1–10]. Acute CRAO is an emergency, should be considered a cerebral infarction of the

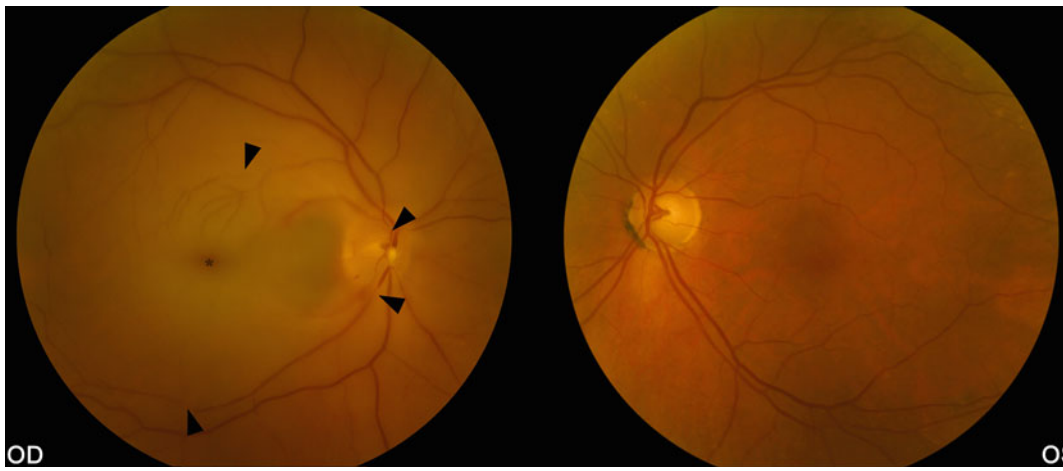

Fig. 5.3 Acute central retinal artery occlusion in the right eye (shown on the *left*). Note the attenuated central retinal artery with segmental narrowing in the right eye (*arrows*) compared with the left eye. The ischemic retina is edematous and appears whitish compared to the left eye and there is a *cherry-red spot* (*)

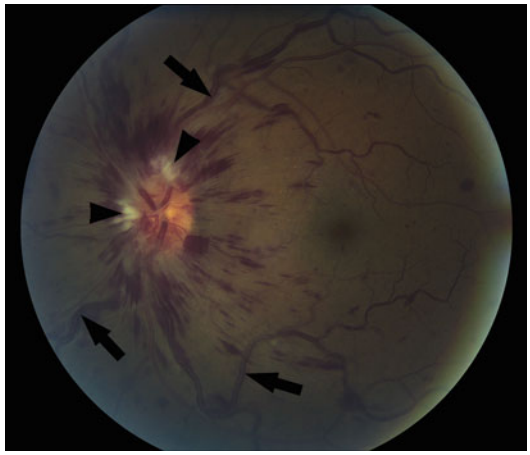

Fig. 5.4 Acute central retinal vein occlusion in the left eye. There are numerous flame retinal hemorrhages, the veins are dilated (*arrows*), and there are cotton wool spots (*arrow heads*) and optic nerve head edema

anterior circulation, and should be evaluated similarly. In patients older than 50 years, giant cell arteritis must also be ruled out [11]. Acute treatments for CRAO are limited, but there are studies evaluating intravenous or intra-arterial thrombolysis in acute CRAO, and stroke neurologists are often consulted to determine whether thrombolysis may be considered in selected CRAO patients presenting within a few hours of visual loss.

Numerous other retinal disorders involving the macula may produce central visual loss, but are usually not associated with an RAPD. Central retinal vein occlusion (Fig. 5.4) is also a cause of painless monocular vision loss, which is usually not associated with neurologic disorders. Age-related macular degeneration is a common cause of acute central visual loss in the elderly; these patients often also have a history of progressive monocular or binocular visual loss with metamorphopsia [12]. Acute worsening of vision in one eye is usually related to bleeding of a macular neovascular membrane. Central serous retinopathy is a cause of acute painless unilateral central vision loss with no RAPD and a normal-appearing optic nerve, most often occurring in young men. Careful examination of the macula shows a "blister" in the macular region.

Optic Neuropathies

Optic neuropathies typically manifest with decreased visual acuity, altered color vision, and abnormal visual fields. An RAPD is always present when the optic neuropathy is unilateral or asymmetric. Acutely, the optic nerve may be normal (posterior optic neuropathy), or may be swollen (anterior optic neuropathy) (Fig. 5.5). The optic nerve becomes pale 4–6 weeks later regardless of the mechanism. Optic neuropathies with acute or subacute vision loss are often evaluated in the emergency department. These optic neuropathies are best classified by mechanism and the clinical characteristics often allow a diagnosis (Table 5.1). Dedicated optic nerve imaging is often helpful, particularly to demonstrate optic nerve inflammation, infiltration, or compression (Fig. 5.5). However, it is important to emphasize that most brain scans (CT or MRI) do not allow proper evaluation of the optic nerves. A CT of the orbits with contrast, thin cuts, and coronal reconstructions is helpful when emergent MRI cannot be obtained, or in the setting of trauma. An MRI of the orbits with contrast and fat suppression is the most sensitive test to image the optic nerves in the orbits, at the level of the orbital apex and intracranially (see Fig. 5.5b). It is particularly important when an optic nerve sheath meningioma or an orbital apex syndrome is suspected.

Inflammatory Optic Neuropathy (Optic Neuritis)

Isolated optic neuritis is often the first manifestation of multiple sclerosis (MS) and is one of the classic clinically isolated syndromes. However, inflammation of the optic nerve may also occur in association with numerous infectious and noninfectious inflammatory disorders.

Patients with optic neuritis present with acute or subacute painful monocular visual loss. Central vision typically deteriorates over hours or days. In mild optic neuritis, color vision change can be the first or the only visual complaint. Pain on eye movement is a frequent early complaint with

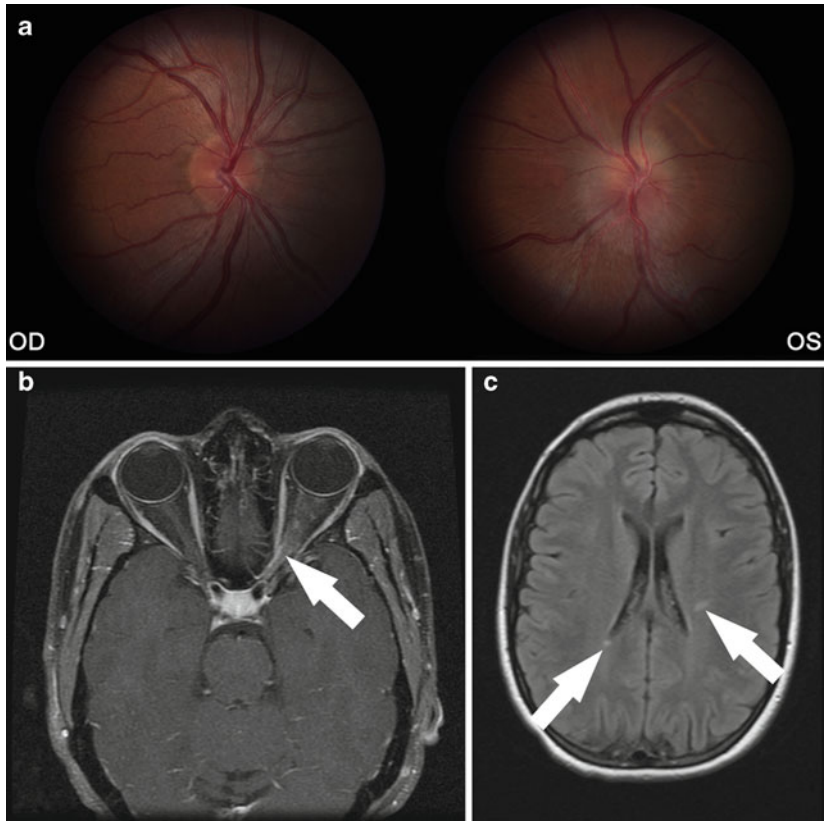

Fig. 5.5 Anterior optic neuritis in the left eye. (**a**) Fundus photograph of both eyes showing mild optic nerve head edema in the left eye (OS) compared with the right eye (OD). (**b**) Axial T1-weighted MRI of the orbits with contrast and fat suppression demonstrating enhancement of the left optic nerve (*arrow*). (**c**) Axial FLAIR MRI of the brain showing two periventricular ovoid lesions suggestive of demyelinating disease

Table 5.1 Most common causes of acute optic neuropathies

Mechanism	Optic neuropathies that often present with acute visual loss in the emergency department
Inflammatory (Optic neuritis)	Clinically isolated syndrome or associated with multiple sclerosis Neuromyelitis optica Not associated with multiple sclerosis: Infectious diseases (syphilis, cat scratch) Systemic inflammatory and autoimmune diseases (sarcoidosis)
Vascular	Ischemic optic neuropathy: Arteritic: Giant cell arteritis Nonarteritic anterior ischemic optic neuropathy
Compressive/infiltrative	Acute compression of the intracranial portion of the optic nerve or of the chiasm: Pituitary mass (pituitary apoplexy) Craniopharyngioma Internal carotid artery aneurysm Any intracranial mass close to the anterior visual pathways
Toxic/nutritional	Methanol poisoning
Hereditary	Leber hereditary optic neuropathy
Traumatic	Direct or indirect mechanism
Raised intracranial pressure	Papilledema
Malignant hypertension	Stage IV hypertensive retinopathy

the visual loss. On examination, there is decreased visual acuity, decreased color vision, and visual field loss centrally [13]. An RAPD will be present if the optic neuritis is unilateral or asymmetric. In isolated optic neuritis associated with demyelinating disease, two-thirds of patients have a normal optic nerve acutely and one-third of patients have moderate optic nerve head swelling (so-called "anterior" optic neuritis or papillitis) (see Fig. 5.5). Optic neuritis with normal-appearing optic nerve acutely is called "retrobulbar" or "posterior" optic neuritis. In all cases, optic nerve head pallor develops 4–6 weeks later.

Evaluation of the patient with optic neuritis varies based on the clinical presentation and the suspected diagnosis. A brain MRI is usually obtained in patients with isolated optic neuritis to look for demyelinating disease (see Fig. 5.5). Blood tests and specific serologies may be obtained depending on the patient's characteristics. Syphilis, cat scratch disease, and sarcoidosis are common alternate causes of optic neuritis. A lumbar puncture may also be useful in this setting. However, in most cases, optic neuritis remains idiopathic or is associated with multiple sclerosis.

In patients with typical isolated optic neuritis, the risk of multiple sclerosis is best predicted by a brain MRI: patients with a normal brain MRI have a risk of multiple sclerosis estimated at 25% at 15 years, whereas those with at least one typical demyelinating lesion on the MRI have a risk close to 70% at 15 years (see Fig. 5.5) [14]. Among the patients with no lesions on the MRI, any of the following features is associated with virtually no risk of multiple sclerosis: male gender, absence of pain, severe optic nerve edema, peripapillary hemorrhages, or macular changes suggesting neuroretinitis. This emphasizes the importance of a funduscopic examination by an ophthalmologist in all cases with presumed optic neuritis.

The visual prognosis of isolated optic neuritis is usually good even without treatment [15]. High-dose intravenous methylprednisolone (1 g/day for 3 days followed by oral prednisone 1 mg/kg/day for 11 days) only accelerates visual recovery, but does not alter long-term visual outcome or the long-term risk of subsequent MS. The Optic Neuritis Treatment Trial showed that 1 mg/kg/day of oral prednisone did not improve visual outcome and doubled the risk of recurrent optic neuritis. Therefore, low-dose oral prednisone is currently not recommended for patients with isolated optic neuritis and intravenous steroids should be discussed on a case-by-case basis.

A subgroup of patients with severe optic neuritis and poor recovery, or with bilateral or recurrent optic neuritis, are found to have positive neuromyelitis optica (NMO) antibodies, even in the absence of transverse myelitis [16].

Neuroretinitis characterizes patients with an anterior optic neuritis associated with retinal exudates, usually in the shape of a star at the macula. In most cases, neuroretinitis is due to an infection such as cat scratch disease or syphilis, or to a noninfectious inflammatory disorder, such as sarcoidosis. Neuroretinitis is not associated with a risk of MS [17]. Treatment of neuroretinitis or infectious optic neuritis depends on the underlying disease.

Ischemic Optic Neuropathy

Ischemic optic neuropathies are classified into anterior ischemic optic neuropathy (AION), in which case there is always optic nerve head swelling acutely (Fig. 5.6), and posterior ischemic optic neuropathy (PION), in which the posterior part of the optic nerve is ischemic with normal-appearing optic disk acutely [18]. AION is much more common than PION, the latter remaining a diagnosis of exclusion. Ischemic optic neuropathies are also classified as "nonarteritic" and "arteritic" (most often associated with giant cell arteritis). Ischemic optic neuropathies present with painless, acute or subacute visual loss with visual field defects and an RAPD; 4–6 weeks later, the optic nerve becomes pale.

Nonarteritic AION (NAION) is the most common form of ischemic optic neuropathy, affecting between 2 and 10 individuals per 100,000. The main risk factor is a small crowed optic disk with no cup (so-called disk at risk) (see Fig. 5.6), but

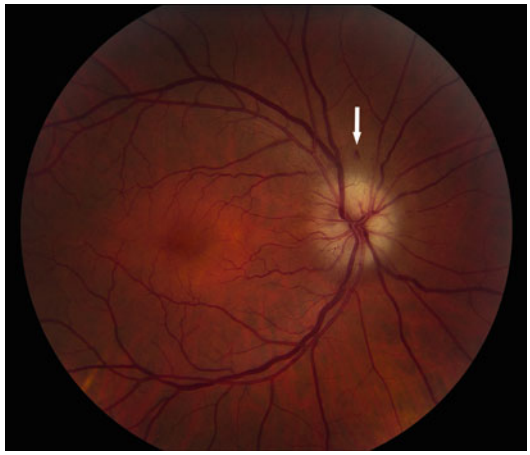

Fig. 5.6 Anterior ischemic optic neuropathy in the right eye. There is an optic nerve head edema, worse superiorly, and a small peripapillary hemorrhage superiorly. The patient had an inferior altitudinal visual field defect

other disk anomalies such as optic nerve head drusen and papilledema can also predispose to NAION [19]. Most patients with NAION are at least 50 years of age and have at least one cardiovascular risk factor. NAION is a small vessel disease involving the short posterior ciliary arteries. It is not embolic and there is no increased risk of cerebrovascular disease in patients with NAION. The pathophysiology involves local arteriolosclerosis involving small vessels, in addition to the "disk at risk." Therefore, although atheromatous vascular risk factors should be identified and aggressively treated, search for a carotid or cardiac source of emboli is usually not necessary in patients with isolated NAION. There is currently no proven treatment for ischemic optic neuropathies, and the only emergency in evaluating a patient with AION or PION is to rule out giant cell arteritis [19]. Indeed, giant cell arteritis should always be considered in all patients older than 50 years with AION or PION, and blood tests looking for a biologic inflammatory syndrome need to be obtained emergently. High-dose steroids are initiated only in patients in whom there is high clinical suspicion of giant cell arteritis, and a temporal artery biopsy should be subsequently obtained in these patients [20]. Administration of high doses of intravenous steroids at the beginning of treatment for giant cell arteritis may decrease the duration of treatment and the total dose of steroids used. However, the treatment remains mostly empirical with very few clinical trials available.

Traumatic Optic Neuropathy

Monocular visual loss after head trauma can result from a direct (when there is direct trauma to the optic nerve by penetrating orbital trauma or optic canal fracture) or indirect traumatic optic neuropathy [4]. These patients often have associated brain and systemic injuries, and recognition of vision loss is often delayed if there is no external sign of ocular injury. Identification of an RAPD in a sedated or unconscious patient may be the only evidence of traumatic optic neuropathy and should be looked for systematically in all head trauma patients. Visual loss may be isolated, with a normal-appearing or swollen optic nerve acutely. There may be associated signs suggesting ocular rupture, dislocation of the optic nerve, or orbital trauma with proptosis, ophthalmoplegia, and elevated intraocular pressure. Orbital imaging with a CT without contrast is essential to rule out an orbital fracture or an orbital hematoma, which may require immediate treatment. An ophthalmologist must perform an immediate detailed examination when there is suspected ocular or orbital trauma. The treatment of direct traumatic optic neuropathies is usually surgical, whereas indirect traumatic optic neuropathies are usually observed. There is evidence that steroids are not only not useful in this subgroup of patients, but also potentially harmful, particularly in the setting of associated brain and systemic injuries [4].

Compressive Optic Neuropathy

Patients with compressive optic neuropathies classically develop progressive uni- or bilateral optic neuropathies. However, many of these patients are not aware of insidious visual loss and present emergently when visual loss worsens, involves central vision, or keeps them from

reading or driving. These patients already have a pale optic nerve at presentation. More rarely, sudden vision loss can result from compressive optic neuropathy. Most often, the lesion involves the orbital apex (metastases and fungal lesions are the most classic) or the intracranial optic nerve and chiasm (pituitary tumors, especially with apoplexy, ophthalmic artery aneurysms, and craniopharyngiomas are the most common). Associated signs such as an orbital syndrome and ocular motor cranial nerve palsies help localize the lesion to the orbital apex or the intracranial portion of the optic nerve, respectively. Emergent evaluation with dedicated MRI of the brain and the orbits with contrast and fat suppression is indicated. MRA or CTA should be obtained when an aneurysm is suspected or when the MRI is normal.

Acute Bilateral Optic Neuropathies

Rarely, simultaneous bilateral optic neuropathies may occur with acute binocular visual loss. These patients are usually severely visually disabled and often present to the emergency department. Because both optic nerves are affected, there may not be an RAPD on examination. When the optic nerves appear normal acutely (such as from bilateral posterior optic neuropathies), the diagnosis may be difficult and relies on pupil examination (which are sluggish in response to light) and visual field testing.

Bilateral inflammatory optic neuritis, with or without disk edema, should suggest an infectious or inflammatory disorder and should prompt a more extensive evaluation than isolated unilateral optic neuritis. A lumbar puncture is usually performed, looking for a meningeal process; sarcoidosis and neuromyelitis optica are classic causes.

Bilateral simultaneous ischemic optic neuropathies in patients older than 50 are highly suggestive of giant cell arteritis, and erythrocyte sedimentation rate and C-reactive protein should be systematically obtained in the emergency department [18].

Pituitary apoplexy with sudden chiasmal and optic nerve compression is also a classic cause of bilateral optic neuropathies (Fig. 5.7). Most patients also have headaches, sometimes with abnormal extraocular movements and altered mental status.

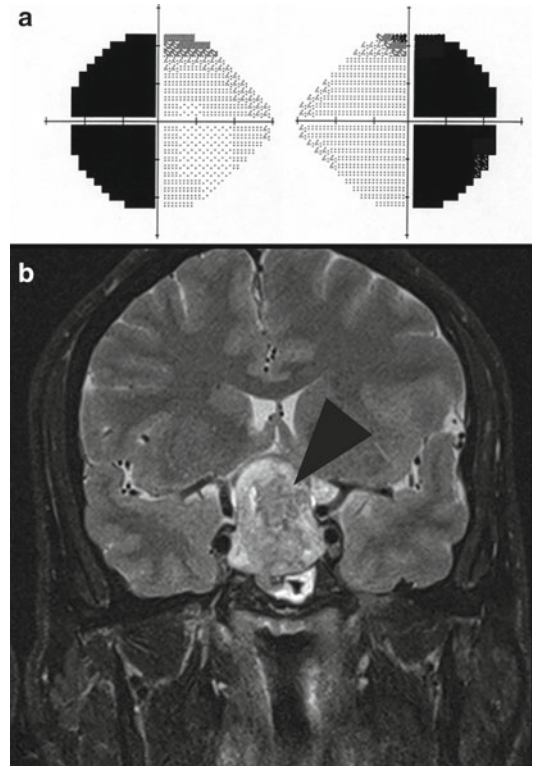

Fig. 5.7 Acute binocular visual loss with bitemporal hemianopia from pituitary apoplexy. The patient also had headaches and diplopia with a left third nerve palsy. (**a**) Humphrey visual fields showing a bitemporal hemianopia. (**b**) Coronal T2-weighted MRI demonstrating a large pituitary mass (*arrowhead*) with chiasmal compression and cavernous sinus compression

Hypertensive retinopathy with bilateral optic nerve head edema can also produce acute or subacute bilateral visual loss (Fig. 5.8).

In most cases, raised intracranial pressure with bilateral papilledema produces slowly progressive visual loss with secondary optic atrophy, rather than acute or subacute visual loss. However, fulminant idiopathic intracranial hypertension or acute causes of raised intracranial pressure such as cerebral venous thrombosis can cause severe bilateral papilledema and rapidly progressive bilateral visual loss (Fig. 5.9) [21, 22].

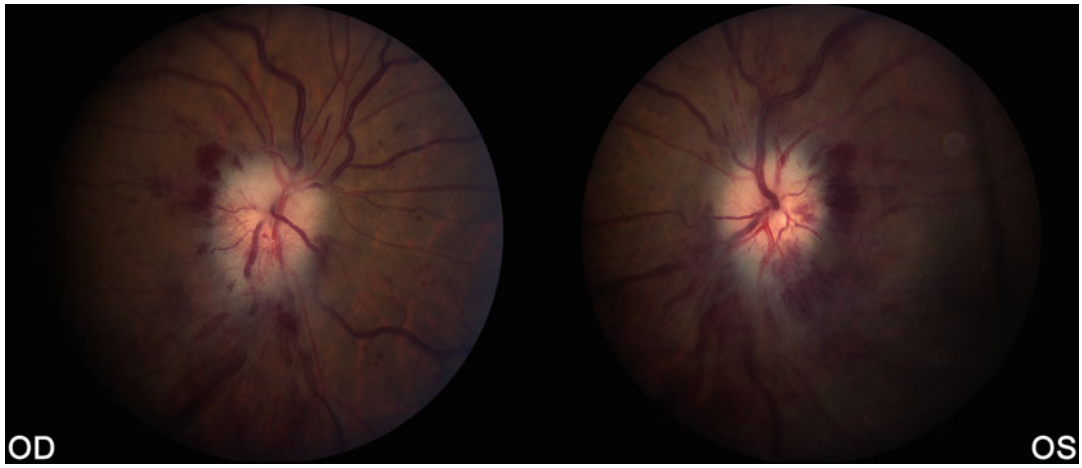

Fig. 5.8 Hypertensive retinopathy with bilateral optic nerve edema and retinal hemorrhages. The retinal arteries are attenuated. Blood pressure was 210/130 mmHg. This is consistent with stage IV hypertensive retinopathy

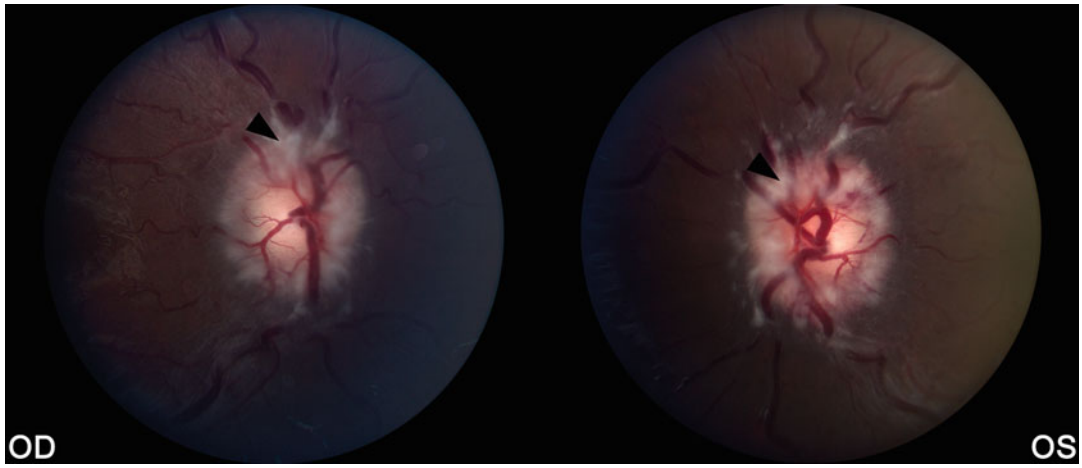

Fig. 5.9 Bilateral severe optic nerve edema consistent with papilledema (from raised intracranial pressure). The optic nerves are elevated with numerous cotton wool spots (*arrows*), and severe dilation of the veins. The patient had thrombosis of the superior sagittal sinus with elevated CSF opening pressure

Leber hereditary optic neuropathy may present with acute bilateral optic neuropathies and profound visual loss [23]. The visual loss is isolated and there is no pain. Brain and orbit MRIs are typically normal without optic nerve enhancement. The diagnosis should be suspected in any patient with bilateral or rapidly sequential painless optic neuropathies, especially if the patient is a young man with a family history of visual loss on the maternal side, and absence of visual recovery. Mitochondrial DNA mutations are routinely tested on a blood sample.

Nutritional and toxic optic neuropathies are typically bilateral and slowly progressive. Acute visual loss can occur after ingestion of methanol (homemade alcohol or antifreeze). The optic nerves usually appear swollen acutely and patients often have associated neurologic signs with confusion and altered mental status [24]. The visual prognosis is poor.

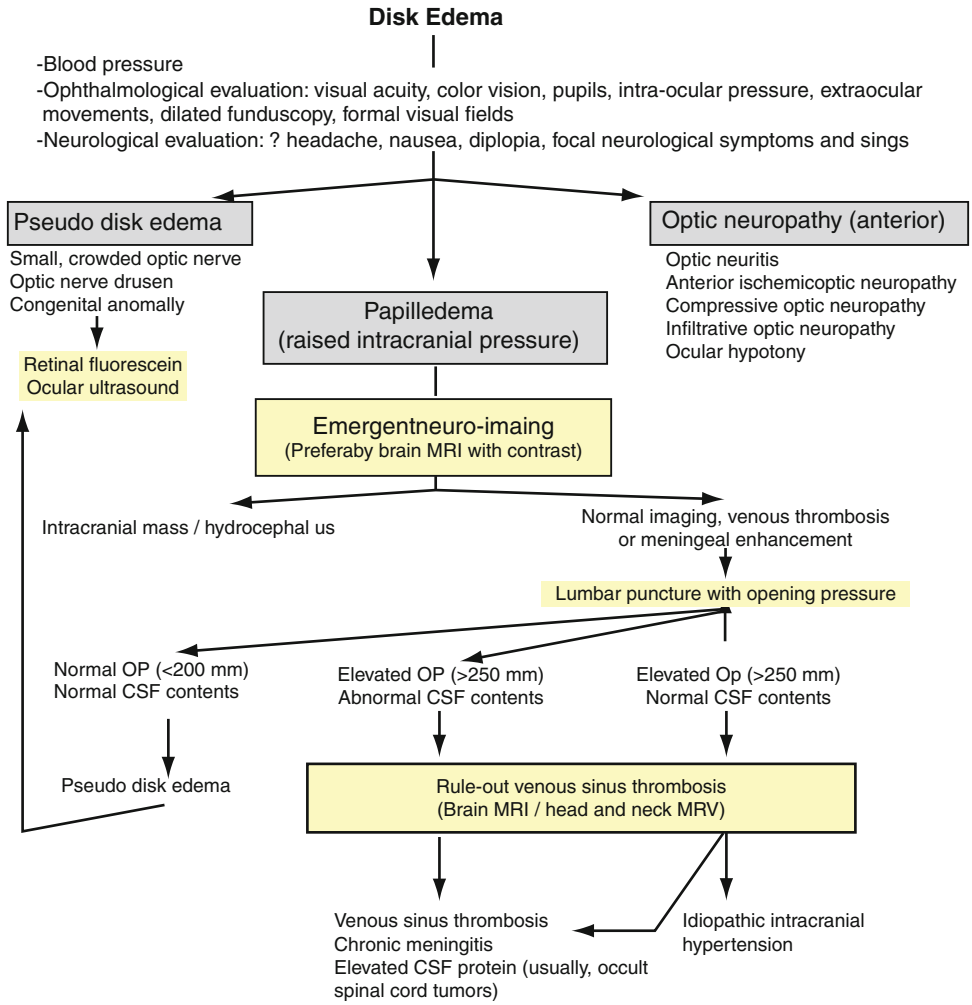

Fig. 5.10 Diagram detailing the diagnosis of disk edema

Bilateral Optic Nerve Edema

Bilateral optic nerve edema may be the result of bilateral anterior optic neuropathies, raised intracranial pressure (i.e., papilledema), or systemic hypertension (stage IV hypertensive retinopathy).

Patients with bilateral anterior optic neuropathies have visual acuity loss, decreased color vision, and abnormal visual fields. Classic causes include bilateral anterior optic neuritis and anterior ischemic optic neuropathies.

When there is bilateral disk edema and central visual acuity is normal, papilledema from raised intracranial pressure should be suspected. All causes of raised intracranial pressure can produce papilledema, which is associated with progressive visual field constriction, secondary optic atrophy, and irreversible visual loss if intracranial hypertension is not timely treated. Indeed, visual loss is the main complication of idiopathic intracranial hypertension and is often encountered in patients with cerebral venous thrombosis (see Fig. 5.9), intracranial mass lesions, or unrecognized hydrocephalus, emphasizing the importance of systematically looking at the fundus of all patients with chronic headaches (Fig. 5.10).

Malignant systemic hypertension (or hypertensive crisis) is often associated with bilateral optic nerve head edema (see Fig. 5.8). There are usually also retinal and vascular changes suggestive of hypertensive retinopathy, such as attenuation of retinal arteries, retinal hemorrhages, and retinal exudates (hypertensive retinopathy stage IV).

Binocular Vision Loss from Chiasmal Lesions

Acute binocular visual loss may result from simultaneous damage to the intracranial portions of the optic nerves, often in association with chiasmal compression.

Pituitary tumors, sphenoid wing meningiomas, and craniopharyngiomas are the most common causes of the chiasmal syndrome. Pituitary apoplexy is a classic cause of acute chiasmal syndrome often associated with headaches, whereas other intracranial processes usually present with more insidious, progressive visual loss. The finding of a bitemporal visual field defect—the hallmark of the chiasmal syndrome—requires immediate brain imaging in patients with acute visual changes (see Fig. 5.7). Internal carotid artery aneurysms can also produce compressive chiasmal syndromes.

Binocular Vision Loss from Retrochiasmal Lesions

A lesion of the retrochiasmal visual pathways (optic tract, lateral geniculate body, visual radiations, or occipital cortex) classically produces a contralateral homonymous hemianopia (Fig. 5.11) [1, 25, 26]. Visual acuity should be normal in each eye, unless there is superimposed damage to the anterior visual pathways. In cases of bilateral injury (most often bilateral occipital lobe lesions), visual acuity may be decreased, but the amount of visual acuity loss is symmetric in both eyes. Any central nervous system disorder involving both occipital lobes may produce bilateral visual loss from so-called cerebral blindness (Table 5.2).

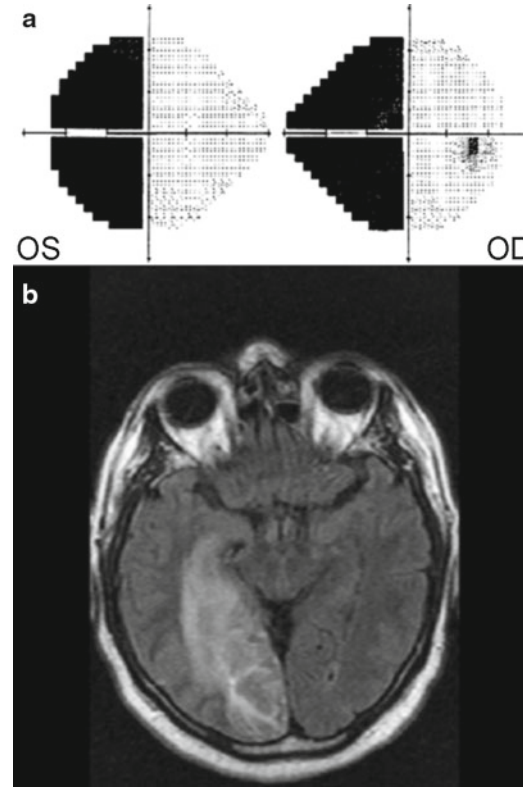

Fig. 5.11 Left homonymous hemianopia secondary to a right occipital infarction. (**a**) Humphrey visual fields showing a complete left homonymous hemianopia. (**b**) Axial FLAIR MRI of the brain showed a right occipital infarction in the territory of the right posterior cerebral artery

A complete homonymous hemianopia (see Fig. 5.11) has no other specific localizing value than the contralateral retrochiasmal visual pathways, but associated symptoms and signs are very helpful in localizing the lesion along the intracranial visual pathways. Optic tract lesions produce a contralateral RAPD, whereas parietal lesions are associated with abnormal optokinetic nystagmus. Congruous incomplete homonymous hemianopias (when the two abnormal fields are similar in both eyes) are most suggestive of an occipital lesion, whereas incongruous homonymous hemianopias suggest a lesion along the more anterior optic radiations. The most common cause of an isolated homonymous hemianopia is a stroke (most often a posterior cerebral artery distribution infarction) (see Fig. 5.11) [27].

Table 5.2 Common neurologic causes of acute binocular visual loss (producing either a homonymous visual field defect or binocular "cerebral" visual loss)

Cerebral causes of acute visual loss
• Vascular – Occipital infarction or hemorrhage – Optic radiations or optic tract infarction or hemorrhage – Superior sagittal venous sinus thrombosis with occipital venous infarction – Arteriovenous malformation involving the visual pathways • Intracranial mass – Any mass involving the intracranial visual pathways • Occipital seizures • Hypoglycemia • Multiple sclerosis • Leukoencephalopathies • Posterior reversible encephalopathy syndrome (PRES) • Hypertensive encephalopathy • Trauma • Carbon monoxide intoxication

Transient Visual Loss

The most important step in evaluating a patient with transient visual loss is to establish whether the visual loss is monocular (a disorder of the eye or the optic nerve) or binocular (a disorder affecting the chiasm or retrochiasmal visual pathways) (Table 5.3).

Deciding whether an episode of transient visual loss occurred in one eye or both is not always easy. Very few patients realize that binocular hemifield (homonymous) visual field loss affects the fields of both eyes. They will usually localize it to the eye that lost its temporal field. The best clues to the fact that transient visual loss was actually binocular are reading impairment (monocular visual loss does not impair reading unless the unaffected eye had prior vision impairment) and visual loss confined to a lateral hemifield (i.e., to the right or left of midline with "respect" of the vertical meridian). Monocular visual loss does not usually cause this pattern of visual loss.

A detailed ocular examination is essential in order to find clues that may help understand the mechanism of visual loss, such as narrow anterior chamber, elevated intraocular pressure, abnormal pupil, retinal emboli (Fig. 5.12), retinal ischemia, optic nerve edema, or residual visual field defect.

Table 5.3 Causes of transient visual loss

Monocular	Binocular
Eye Ocular surface Anterior segment Angle-closure glaucoma	*Bilateral anterior visual pathways* Ocular disorders affecting both eyes Hyperglycemia Bilateral optic neuropathies
Retina/choroid Ischemia	*Intracranial visual pathways* Chiasmal compression
Optic nerve Ischemia (giant cell arteritis) Compression Swelling, drusen, crowding	Any transient process affecting the occipital lobes or the intracranial visual pathways (most common are migrainous visual aura, occipital seizures, and occipital transient ischemic attacks)

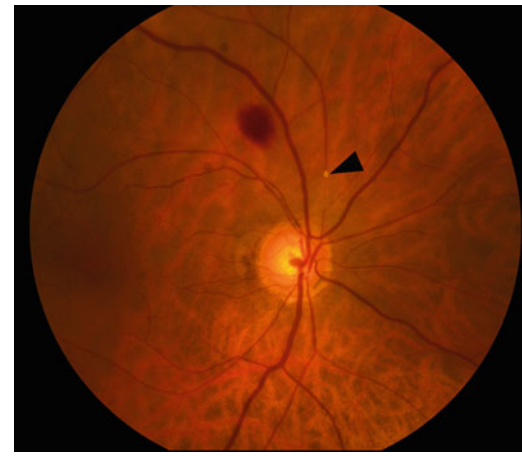

Fig. 5.12 Branch retinal arterial embolus in a patient with an episode of transient loss of vision in the right eye. Fundus photograph of the right eye showing a retinal cholesterol embolus (*arrow head*) from a carotid artery atheroma. There is a large intraretinal hemorrhage superiorly related to retinal ischemia

Monocular Transient Visual Loss

Neurologists are often called to evaluate patients with transient monocular visual loss (TMVL).

Table 5.4 Differential diagnosis of transient monocular visual loss (TMVL)

Vascular
Orbital ischemia (ophthalmic artery)
Retinal ischemia (central retinal artery and its branches, central retinal vein)
Optic nerve ischemia (short posterior ciliary arteries/ophthalmic artery)
Choroidal ischemia (posterior ciliary arteries)
Ocular diseases
Anterior segment disorders (dry eyes, keratoconus, hyphema, spontaneously resolving attacks of angle-closure glaucoma, serous retinal detachment…)
Optic nerve disorders
Papilledema (transient visual obscurations)
Optic disk drusen (transient visual obscurations)
Congenitally anomalous optic disk (transient visual obscurations)
Optic nerve compression (gaze-evoked TMVL)
Uhthoff phenomenon (demyelination)

However, it is important to keep in mind that numerous ocular conditions can also produce TMVL and need to be ruled out by a detailed ocular examination before assuming that the mechanism of TMVL is vascular (see Table 5.3).

Ocular Causes of Monocular Transient Visual Loss

Most ocular disorders can produce fluctuations in vision and may be described as "TMVL" by patients. Ocular disorders usually produce transient blurry vision rather than complete blackout of vision as in vascular TMVL. Blurry vision worsened by reading (during which blinking is reduced) and improving with blinking or rubbing the eye is highly suggestive of dry eyes and other corneal surface disorders causing an abnormal tear film. Acute increase in intraocular pressure can produce transient visual changes, often described as halos around lights and associated with eye pain. Such episodes are suggestive of spontaneously resolving angle-closure glaucoma precipitated by dim light in hyperopic patients, or pigmentary dispersion syndrome after exercise in young myopic patients. In patients with diabetes mellitus, acute hyperglycemia can cause blurry vision lasting hours to days from transient refractive or macular changes. Anomalous optic disks such as papilledema, drusen, and tilted optic disks can produce recurrent episodes of TMVL lasting a few seconds (transient visual obscurations), often precipitated by changes in posture. Orbital tumors may present as episodes of monocular TMVL precipitated by eye movements in a specific gaze direction.

Mechanisms of Vascular Transient Monocular Visual Loss

Vascular TMVL may result from a retinal transient ischemic attack (TIA) in the carotid circulation and should be managed emergently, similar to hemispheric TIAs, in order to reduce the risk of permanent visual loss, stroke, or cardiovascular death (Table 5.4) [28, 29]. Vascular TMVL may result from emboli in the ophthalmic artery or in the central retinal artery, from ocular hypoperfusion, or more rarely from central retinal artery spasm [28]. Vascular TMVL resulting from optic nerve ischemia is rare and is highly suggestive of giant cell arteritis, in which case the optic nerve is usually swollen. Rarely, TMVL may inaugurate a central retinal vein occlusion, with dilated veins on funduscopic examination.

The description of the visual loss, its duration, and the ocular examination (particularly of the ocular fundus) are helpful in understanding the mechanism. Findings of retinal arterial emboli suggest a carotid, aortic arch, or cardiac source of emboli (see Fig. 5.12). Retinal hemorrhages and dilation of the veins suggest chronic ocular hypoperfusion and ocular ischemic syndrome. Optic disk edema suggests optic nerve ischemia and should prompt immediate treatment and workup for giant cell arteritis (see Fig. 5.6).

Table 5.5 Characteristics of the three most common causes of binocular transient visual loss

	Migrainous visual aura	Occipital seizures	Occipital transient ischemic attack
Visual symptoms	Positive Very rich, moving Often black and white, scintillating, shimmering, jagged edges	Positive Simple visual phenomena (phosphenes, bubbles) Colored	Negative (hemianopia or blindness)
Progression of symptoms	Typical migrainous March, with progression of symptoms over time	Usually not progressive	Sudden onset and disappearance
Duration of visual symptoms	Typically 20–30 min. Less than an hour	Usually brief (seconds) Often repeated	A few minutes
Associated symptoms	Migrainous headache typically follows the aura Visual aura may be followed by other migrainous aura (mostly sensory)	Often none May be associated with other seizures	Brow headache possible at the time of visual symptoms Vertebrobasilar ischemia: Vertigo, dizziness Imbalance Diplopia Bilateral extremity weakness

Association of TMVL and ipsilateral painful Horner syndrome points to internal carotid artery disease and is highly suggestive of internal carotid artery dissection. Often, however, the ocular examination is normal and the patient is evaluated for all causes of retinal TIAs. All patients over the age of 50 require emergent workup for giant cell arteritis.

Binocular Transient Visual Loss

Binocular transient visual loss usually results from intracranial processes involving the chiasmal and retrochiasmal visual pathways. More rarely it can be related to bilateral ocular disorders or to transient visual obscurations associated with papilledema (see Table 5.3). Migrainous visual aura, occipital seizures, and occipital TIAs are the most classic causes of binocular transient visual loss, and are usually identified based on the patient's description (Table 5.5).

Migrainous Visual Aura

Migrainous visual aura is the most common cause of transient binocular visual loss and is usually easily diagnosed based on the patient's description. Patients describe a scintillating scotoma expanding over several minutes into a visual field, surrounded by jagged, luminous, shimmering edges. The scotoma can lead to a complete hemianopia and disappears gradually. A migraine headache characteristically follows the scotoma but some patients experience the visual aura of migraine without associated headache. The vision returns to normal within 20–30 min.

Occipital Seizures

Occipital seizures typically produce brief binocular positive visual phenomena often described as flashing lights or bubbles. They typically last only a few seconds, but they are usually repetitive and are relatively stereotyped in the same patient.

Occipital Transient Ischemic Attack

Episodes of transient, complete binocular visual loss may represent a TIA in the distribution of the basilar artery or the posterior cerebral arteries. A unilateral occipital TIA manifests as a transient homonymous hemianopia whereas a bilateral occipital TIA manifests as transient "cortical blindness." As opposed to migraine, hemianopic events of ischemic origin are typically sudden in

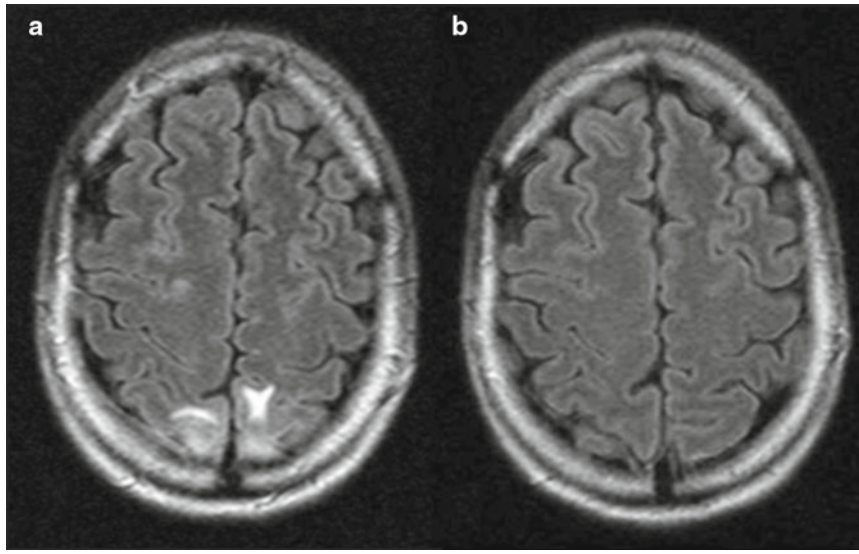

Fig. 5.13 Posterior reversible encephalopathy syndrome (*PRES*) secondary to hypertensive crisis. The patients presented with headaches and binocular visual loss. (**a**) Axial FLAIR MRI showing white matter hyperintense lesions involving both parieto-occipital lobes. (**b**) Six weeks after treatment of the hypertension, the MRI has normalized (and the vision has returned to normal)

onset and last only a few minutes. There may be associated headache, especially over the brow contralateral to the visual field loss, but the pain is usually coincident with the visual loss, rather than following the visual loss as in migraine. Other symptoms of vertebrobasilar ischemia are often present, such as vertigo, dizziness, imbalance, diplopia, or bilateral extremity weakness.

Posterior Reversible Encephalopathy Syndrome

Posterior reversible encephalopathy syndrome (PRES) classically produces acute bilateral visual loss lasting hours or days, usually associated with headaches and altered mental status. Malignant systemic hypertension, medications such as cyclosporine or tacrolimus, and various metabolic disorders are classic causes of PRES. Brain MRI shows T2 hyperintense lesions involving most often the white matter of both occipital lobes (Fig. 5.13). Treatment of the underlying disorder usually results in dramatic improvement of visual function within days, followed by complete resolution of the MRI changes within weeks [30].

Conclusion

Visual loss is a common symptom in neurologic emergencies. Simple beside examination (including ocular funduscopic examination) is crucial in localizing the lesion and identifying ocular changes such as retinal emboli or optic nerve head edema that may require specific intervention and management.

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Diplopia, Third Nerve Palsies, and Sixth Nerve Palsies

6

Janet C. Rucker

Abstract

Ocular motor deficits are common clinical manifestations of neurological emergencies, with third (oculomotor) and sixth (abducens) paresis among the most frequent. This chapter focuses on recognition, diagnosis, and treatment of these cranial neuropathies in true neurological emergencies that carry a high risk of major morbidity or mortality if left undiagnosed. Emergencies discussed include alterations in intracranial pressure, intracranial aneurysms, fungal sinusitis, giant cell arteritis, meningitis, pituitary apoplexy, stroke, and Wernicke's encephalopathy.

Keywords

Microvascular cranial mononeuropathy • Posterior communicating artery aneurysm • Sixth nerve palsy • Third nerve palsy

Introduction

Ocular motor deficits are common clinical manifestations of neurological emergencies. In fact, they are often the distinctive clinical feature facilitating accurate lesion localization. Two of the most common ocular motor deficits, third nerve (oculomotor, CN III) palsies and sixth nerve (abducens, CN VI) palsies, are the focus of this chapter. Ocular misalignment from dysfunction of these nerves causes binocular diplopia that resolves completely with monocular covering of either eye.

Comprehensive coverage of the myriad causes of third and sixth nerve palsies is not the goal of this chapter and can be found in other sources [1, 2]. Rather, the focus is on the relationship between these cranial nerve palsies and true neurological emergencies (Table 6.1) with high immediate risk of mortality or morbidity if left undiagnosed. As with most neurological signs, accurate localization is achieved by consideration of the sign and "the company it keeps." A patient with a third or sixth nerve palsy should be questioned regarding headache, eye pain, vision loss in one eye, facial numbness or tingling, stiff neck, fever, confusion, and changes in level of consciousness. Brief attention is given to third and sixth nerve palsies in combination with other

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Table 6.1 True neurologic emergencies that cause third and sixth nerve palsies

Alterations in intracranial pressure (ICP) High ICP—intracranial space occupying lesion, venous sinus thrombosis Low ICP—spontaneous intracranial hypotension
Intracranial saccular aneurysms (especially posterior communicating artery aneurysms causing third nerve palsies)
Fungal sinusitis with extension to the orbital apex or cavernous sinus
Giant cell arteritis
Meningitis Infectious (fungal, bacterial)
Pituitary apoplexy
Stroke (ischemic and hemorrhagic)
Wernicke's encephalopathy

signs, such as hemiparesis, hemisensory changes, ataxia, and Horner's syndrome; however, the true diagnostic challenge in third and sixth nerve palsies arises when they occur in neurological isolation. Cranial mononeuropathies have multiple benign and spontaneously resolving etiologies; however, clinical prowess is required in determining if and when diagnostic evaluation is warranted to exclude neurologic emergencies.

Epidemiology

Epidemiologic studies on the etiologic incidence of third and sixth nerve palsies vary in analytical approach and study design and, thus, present variable etiologic distributions. Factors that significantly influence etiologic distribution include study population (socioeconomic status, age distribution), study location (inpatient-based versus outpatient tertiary care center versus outpatient population-based studies), inclusion of unilateral versus bilateral ocular motor cranial nerve palsies, and inclusion of neurologically isolated ocular motor nerve palsies versus those associated with other neurological signs. For example, studies including primarily inpatients at tertiary care centers present much higher etiologic percentages of neurologic emergencies than outpatient-based studies, and studies including neurologically nonisolated cranial nerve palsies (such as those with coexisting papilledema) present higher percentages of neoplasm than studies including only neurologically isolated cranial mononeuropathies. In general, these epidemiologic studies are helpful in providing perspective with regard to common causative third and sixth nerve palsy lesions; however, they provide little guidance in assisting the clinician with prompt recognition of neurologic emergencies.

Third Nerve

Third nerve palsies represent approximately 30% of ocular motor cranial nerve palsies, being less common than sixth nerve palsies and more common than fourth nerve palsies [3, 4]. In large retrospective series of third nerve palsies with defined etiologic causes, microvascular ischemia (not a neurologic emergency, see "Diagnosis" section below) was among the most common identified etiologies in most of the series (Table 6.2), representing 17–35% of cases [3–6]. However, aneurysmal and neoplastic causes were nearly equally as common, representing up to 18–19% of cases, and a large percentage of patients in each series had an undetermined etiology. Thirty-four to 61% of posterior communicating artery aneurysms (PComA) are associated with third nerve paresis [7, 8]. In the 1966 series by Rucker, metastatic neoplasms were responsible for 40% of neoplastic cases, with primary intracranial tumors representing the rest [3]. Pituitary adenomas were causative in 28% of neoplastic cases. Neurologic emergencies were included among cases classified as "other," including infectious meningitis, subdural hematoma, and giant cell arteritis [3]. Although each of these diagnoses represented less than 1% of third nerve palsies, they are true emergencies and must be differentiated from benign causes of cranial nerve dysfunction.

The presence or absence of pupillary involvement is critical in the differential diagnosis of the etiology of a third nerve palsy (see "Clinical Features and Diagnosis" sections below); however, the etiologic series in Table 6.2 represent all third nerve palsies, regardless of pupillary function.

Table 6.2 Causes of third nerve palsies

	Trauma	Neoplasm	Vascular[c]	Aneurysm	Undetermined	Other
Rucker 1958 $n=335$	15[a]	11	19	19	28	8
Rucker 1966 $n=274$	12	18	17	18	20	15
Rush 1981 $n=290$[b]	16	12	21	14	23	14
Park 2008 $n=48$	19	6	35	10.5	19	10.5

[a]All numbers given in percentage of the total *n*.
[b]First study following widespread use of head CT imaging.
[c]Specifically, microvascular ischemia.

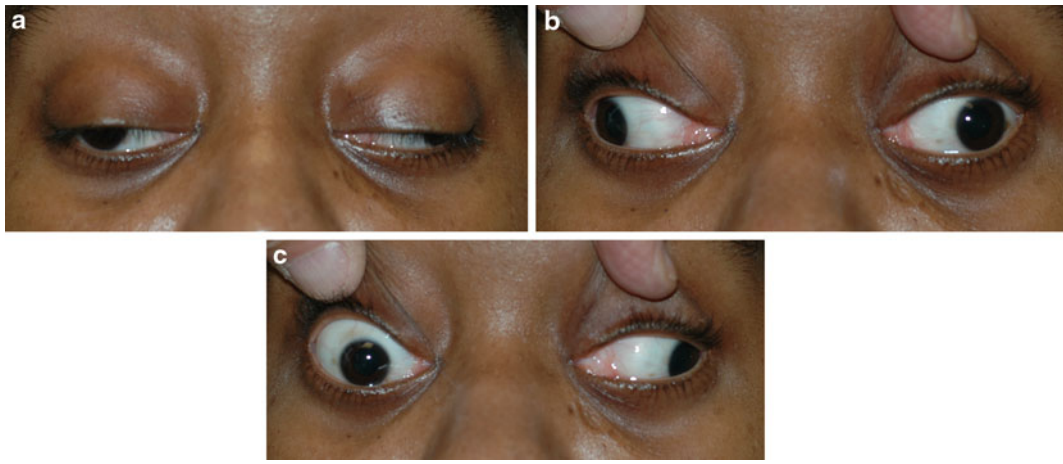

Fig. 6.1 Bilateral third nerve palsies in a 34-year-old woman status-post resection of a midbrain cavernous malformation following midbrain hemorrhage. Pupils were dilated to 8 mm bilaterally and were nonreactive to light; upgaze was almost completely absent in both eyes, and there was minimal depression of each eye. (**a**) Primary position with bilateral ptosis and a large outward deviation of the eyes (exotropia). (**b**) Attempted right gaze reveals full abduction of the right eye (normal sixth nerve function) but completely absent adduction of the left eye. (**c**) Attempted left gaze reveals full abduction of the left eye (normal sixth nerve function) but completely absent adduction of the right eye

Bilateral third nerve palsies (Figs. 6.1 and 6.2) are significantly less common than unilateral third nerve palsies. The series in Table 6.2 included both unilateral and bilateral cases in the etiologic distributions. In the largest case series specifically addressing the frequency of bilateral involvement of a single cranial nerve, bilateral third nerve palsies represented only 5% of 578 cases of simultaneous involvement of single nerve among all 12 cranial nerves [9]. Vascular causes, including subarachnoid and brainstem hemorrhage and brainstem infarction, were the most common etiologies.

Sixth Nerve

Sixth nerve palsies are more common than third or fourth nerve palsies, representing up to 40–50% of ocular motor cranial nerve palsies [3, 4]. In large retrospective series of sixth nerve palsies with defined etiologic causes in patients of all ages, wider variability is seen than in the third nerve palsy series. Of sixth nerve palsies, approximately 30% each are due to microvascular ischemia (not a neurologic emergency, see "Diagnosis" section below) and neoplasm (Table 6.3) and, in most series, between 20 and

30% have an undetermined etiology [3–6, 10–13]. In series dedicated to children, neoplasms were the most common cause of sixth nerve dysfunction and, in many cases, were accompanied by papilledema and nystagmus [14, 15]. In the 1966 series by Rucker, metastatic neoplasms were responsible for 40% of neoplastic cases, with nasopharyngeal carcinoma being the most common [3]. Primary intracranial tumors represented the rest. Pontine gliomas (the majority in children) were the most common primary brain tumor and pituitary adenomas were causative in only 5% of neoplastic cases. Neurologic emergencies were included among the large number of cases classified as "other," including intracranial hypertension, Wernicke's encephalopathy, infectious meningitis, subdural hematoma, and giant cell arteritis. As with third nerve palsies, each of these represented a small percentage of cases, but they are of extreme importance as neurologic emergencies [3, 11].

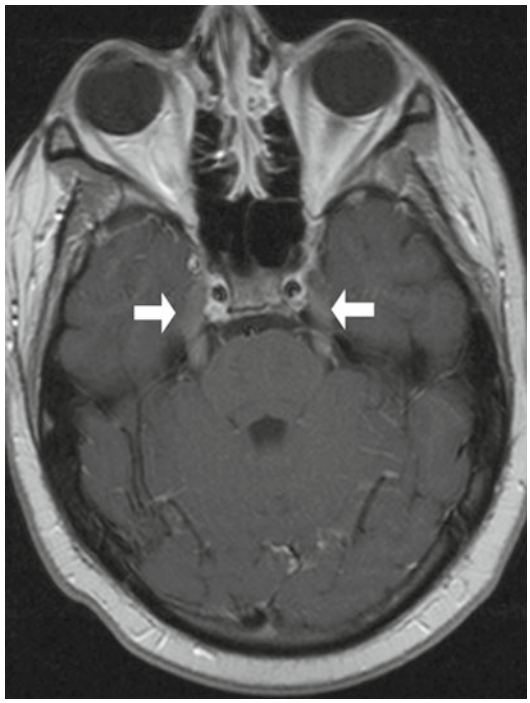

Fig. 6.2 Axial gadolinium-enhanced T1-weighted brain MRI reveals enhancement along the course of both fifth (CV, trigeminal) nerves (*white arrows*) in a patient with systemic lymphoma. On examination, the patient had bilateral loss of facial sensation and bilateral third nerve palsies from involvement of the cavernous sinuses bilaterally

Bilateral sixth nerve palsies (Fig. 6.3) are significantly less common than unilateral sixth nerve palsies, but are much more common than bilateral third nerve palsies. The series in Table 6.3 included both unilateral and bilateral cases without distinction in the etiologic distributions, with exception of the series by Keane, in which etiologies are compared between bilateral sixth nerve palsies (125 cases) and unilateral sixth nerve palsies (143 cases) [11]. In the acute, inpatient setting of this series, the majority of both bilateral and unilateral sixth nerve palsies fell into the "other" category, with subarachnoid hemorrhage (SAH), infection, stroke, and raised intracranial pressure as common etiologies. In the case series

Table 6.3 Causes of sixth nerve palsies

	Trauma	Neoplasm	Vascular[b]	Aneurysm	Undetermined	Other
Rucker1958 $n=545$	16[a]	21	11	6	30	16
Shrader 1960 $n=104$	3	7	36	0	24	30
Rucker 1966 $n=515$	11	31	8	3	22	25
Robertson 1970 $n=133$ (children)	20	39	<1^	2	9	29
Keane 1976 Bilateral VI, $n=125$	10	22	0	0	2	66
Unilateral VI, $n=143$	14	18	2	1	4	61
Rush 1981 $n=419$	17	14	18	3	30	18
Moster 1984 $n=49$ (age <50)	6	16	29	0	22	27
Lee 1999 $n=75$ (children)	12	45	0	0	5	37
Patel 2004 $n=137$	12	5	35	2	26	20
Park 2008 $n=108$	19	5	28	4	24	20

[a]All numbers given in percentage of the total *n*.
[b]Specifically, microvascular ischemia (with exception of Robertson study in children, see notation ^).
^vascular in this case refers to an arteriovenous malformation.

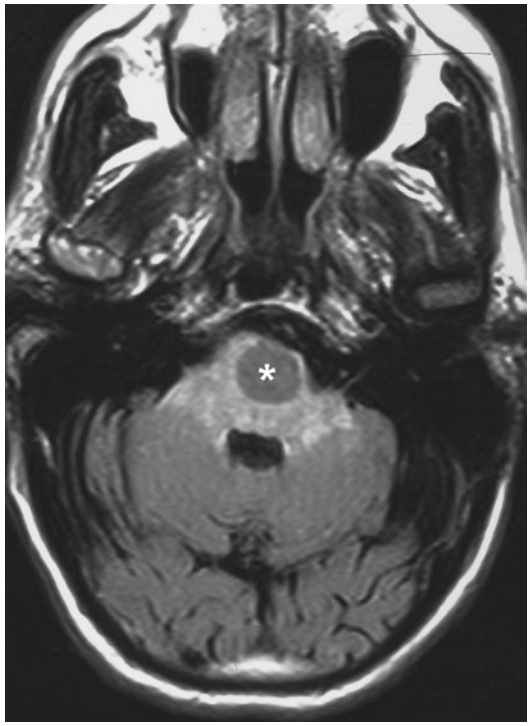

Fig. 6.3 Axial T1-weighted brain MRI through the pons reveals a metastatic lesion with surrounding edema. The patient presented with binocular, horizontal diplopia due to bilateral sixth nerve palsies

specifically addressing the frequency of bilateral involvement of a single cranial nerve, bilateral sixth nerve palsies represented 40% of 578 cases of simultaneous involvement of single nerve among all 12 cranial nerves. Trauma was the most common etiology [9].

Pathophysiology and Anatomy

Third Nerve

Paired third nerve nuclei lie at the level of the superior colliculus ventral to the periaqueductal gray matter. Each nucleus contains inferior rectus, medial rectus, and inferior oblique subnuclei providing ipsilateral innervation; a superior rectus subnucleus providing contralateral innervation; and an Edinger–Westphal nucleus supplying ipsilateral preganglionic parasympathetic output to the iris sphincter and ciliary muscles. A single midline caudal central subnucleus provides innervation to both levator palpebrae superioris muscles.

The third nerve fascicle originates ventrally from each nucleus, passes through the red nucleus and emerges from the ventral midbrain as rootlets in the interpeduncular fossa. The rootlets converge into a nerve trunk that passes through the subarachnoid space and between the superior cerebellar and posterior cerebral arteries. The third nerve travels very near to the anterior segment of the posterior communicating artery (PCom) at its junction with the intracranial internal carotid. In the cavernous sinus, the third nerve is within the lateral dural wall, lateral to the pituitary gland and sella. In the anterior cavernous sinus, it physically separates into superior and inferior divisions, although patterns of pupil and muscle involvement in brainstem lesions suggest that functional division occurs in the midbrain [16–18]. The inferior division innervates the inferior and medial recti, the inferior oblique, and the iris sphincter and ciliary muscles. The superior division innervates the superior rectus and the levator palpebrae superioris. Inferior and superior divisions enter the orbit through the superior orbital fissure. Parasympathetic fibers synapse in the ciliary ganglion in the orbit prior to innervating the iris sphincter and ciliary body.

The most important third nerve neurological emergency occurs as the third nerve passes through the subarachnoid space in close approximation to the PCom at its junction with the internal carotid artery. This is the location of PComA that cause third nerve dysfunction via direct aneurysmal compression of the ipsilateral nerve (Fig. 6.4). Other less common third nerve emergencies include ischemic or hemorrhagic stroke at the level of the midbrain fascicle and unilateral or bilateral third nerve compression in the cavernous sinus from pituitary apoplexy.

Sixth Nerve

Paired sixth nerve nuclei in the dorsal pons in the fourth ventricular floor lie in close proximity to the facial nerve fascicles. Each nucleus contains

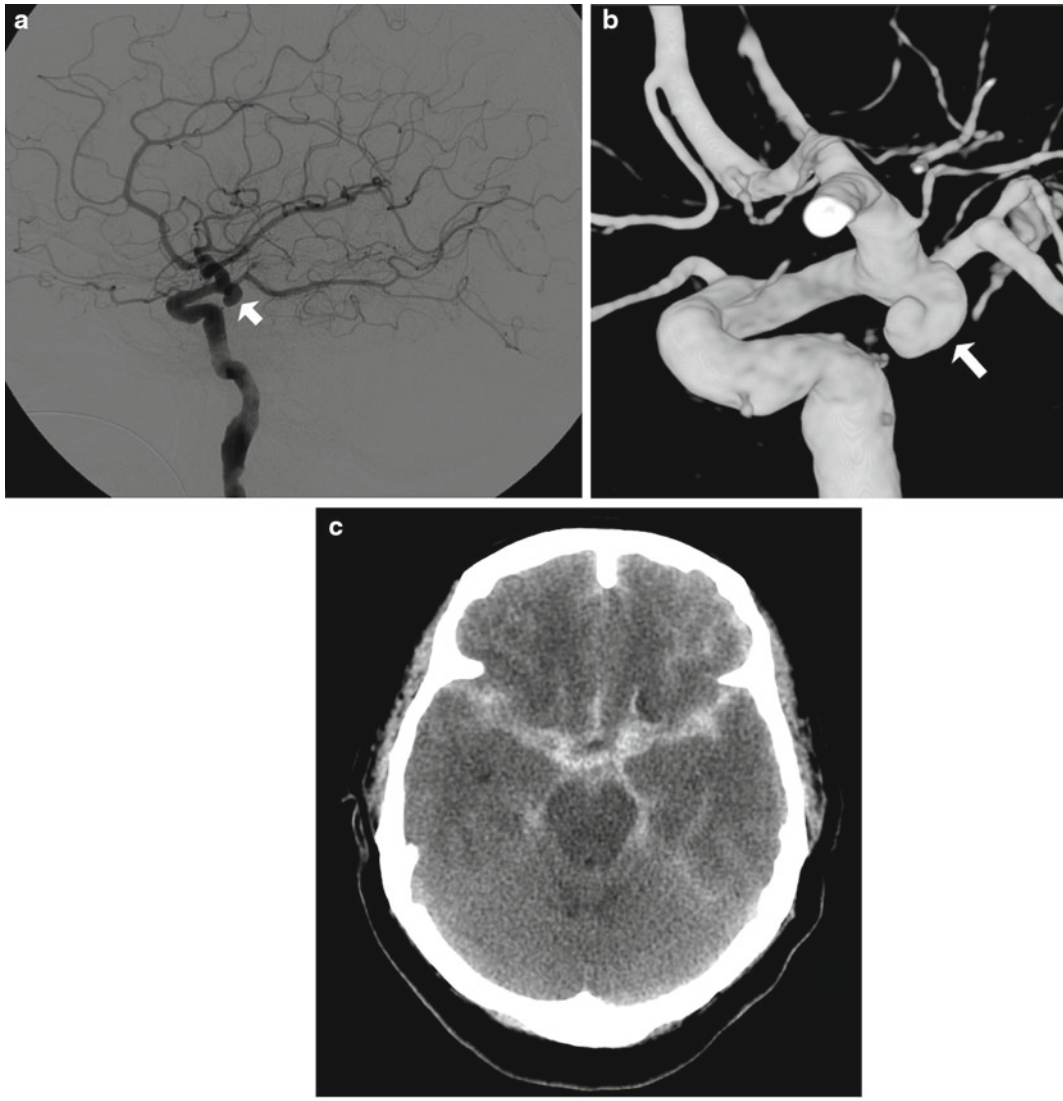

Fig. 6.4 Conventional cerebral angiogram (left internal carotid artery catheterization) reveals a 6–7-mm aneurysm on standard images (**a**) and 3D reconstructed images (**b**) at the junction of the left internal carotid artery and a fetal origin posterior communicating artery. The 55-year-old patient presented with a left third nerve palsy, syncope, severe headache, and confusion. Head CT reveals subarachnoid hemorrhage (**c**) images courtesy of Deborah Carson and Dr. Aman Patel

abducens motoneurons that form the sixth nerve and interneurons that decussate at the nuclear level and ascend in the medial longitudinal fasciculus to the contralateral medial rectus subnucleus of the third nerve nucleus. These interneurons facilitate conjugate horizontal gaze in the direction ipsilateral to the interneuron nuclear origin. From the ventral surface of the nucleus, the sixth nerve fascicle passes through the pons, emerges from the caudoventral pons, and passes through the subarachnoid space. It then ascends near the clivus, pierces the dura, and passes under the petroclinoid (Gruber's) ligament in Dorello's canal. In the cavernous sinus, the sixth nerve is free within the sinus body just lateral to the internal carotid artery. It enters the orbit through the superior orbital fissure to innervate the lateral rectus muscle.

Sixth nerve palsies due to neurological emergencies tend to occur at the level of the sixth

nerve fascicle within the pons or at the level of the sixth nerve as it passes through Dorello's canal. Pontine ischemic or hemorrhagic infarction and Wernicke's encephalopathy affect the former, whereas alterations in intracranial pressure affect the latter.

Clinical Features

Third Nerve

General Clinical Appearance

A third nerve palsy may result in paresis of any third nerve innervated muscle: inferior, superior, or medial recti; inferior oblique; levator palpebrae superioris; or pupillary iris sphincter (Figs. 6.1, 6.5, and 6.6). The structures may be individually affected, affected in any partial combination, or all may be simultaneously affected. When all are simultaneously paralyzed, the classic appearance of this complete third nerve palsy affecting all third nerve innervated structures is an eye that is "down and out" (in other words, an eye that is hypotropic and exodeviated), ptotic, and has a dilated nonreactive pupil. Eye depression (from inferior rectus involvement), elevation (from superior rectus and inferior oblique involvement), and adduction (from medial rectus involvement) are all eliminated in a complete third nerve palsy. Superior divisional third nerve palsies cause ptosis and impaired elevation (especially in an abducted eye position) of the ipsilateral eye, whereas inferior divisional third nerve palsies cause impaired elevation, depression, and adduction with pupillary involvement of the ipsilateral eye.

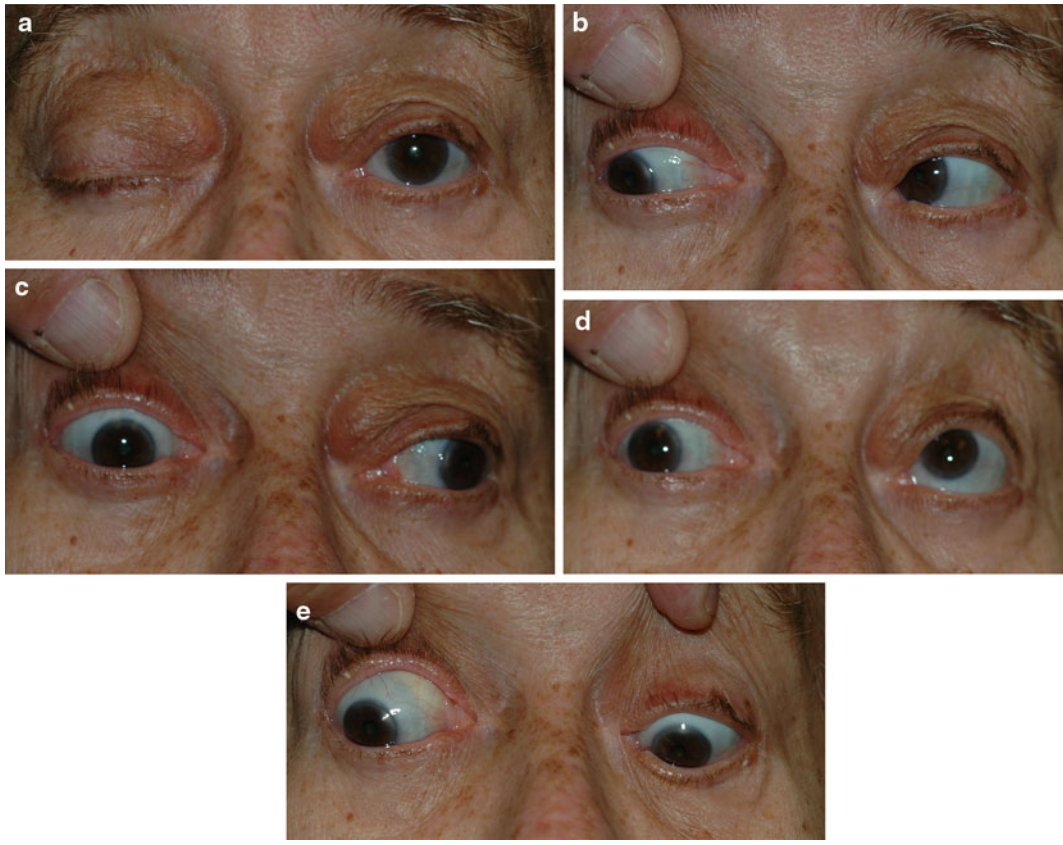

Fig. 6.5 Right third nerve palsy from a right intracavernous carotid artery aneurysm. The pupil was partially affected with the right pupil larger than the left and slightly less reactive to light. (**a**) Central and in position with complete right ptosis. (**b**) Right gaze with normal abduction of the right eye. (**c**) Left gaze with impaired adduction of the right eye. (**d**) Upgaze with absent elevation of the right eye. (**e**) Downgaze with fairly intact depression of the right eye

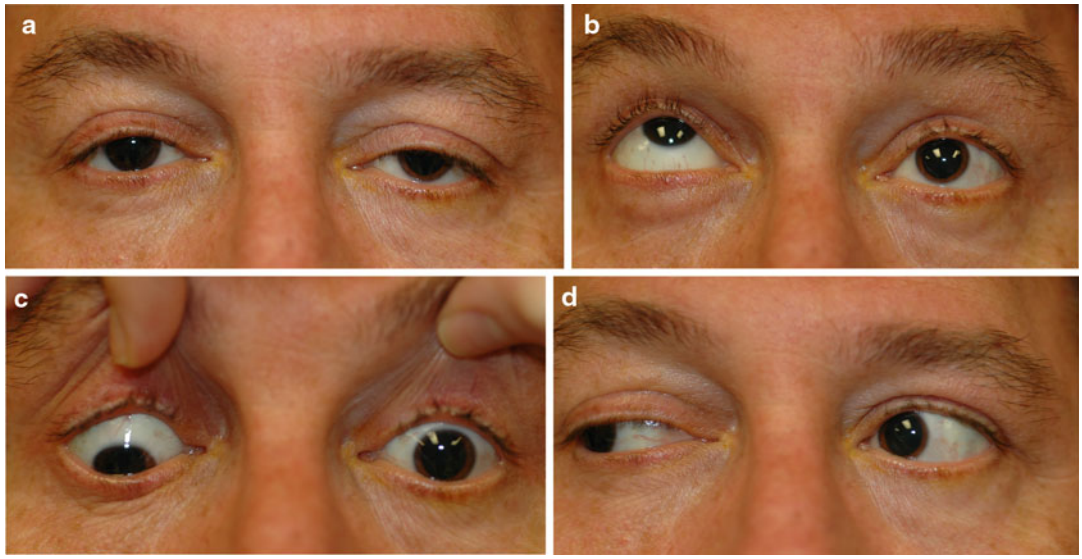

Fig. 6.6 Left third nerve palsy due to a left cavernous sinus meningioma. Left sixth nerve function was intact (not shown). Prior to dilation, there was pupillary involvement (not shown) with 2-mm anisocoria and a large, poorly reactive left pupil. In all photos, pupils are pharmacologically dilated. (**a**) Left ptosis with eyes in central position. (**b**) Minimal elevation of left eye in attempted upgaze. (**c**) Minimal depression of the left eye in attempted downgaze. (**d**) Mild impairment of adduction of the left eye in attempted right gaze. Note the widening of the palpebral fissure upon adduction, consistent with aberrant regeneration

The presence or absence of aberrant regeneration should be specifically sought in the clinical examination of any third nerve palsy. Elevation of the eyelid or constriction of the pupil during adduction or depression of the eye is evidence of aberrant regeneration, or anomalous axonal reinnervation [19, 20]. It is almost always due to third nerve dysfunction caused by a compressive or traumatic etiology (see Fig. 6.6).

It should be determined if the third nerve is affected in isolation. Full neurological examination should be performed. In order to determine that the sixth and fourth nerves are not affected, abduction of the affected eye (sixth nerve function) and intorsion of the abducted eye upon attempted downgaze (fourth nerve function) should be intact.

PCom Aneurysm

PComA (at the junction of the PCom and internal carotid artery) are the etiology of any pupil-involving or partial third nerve palsy (even if not involving the pupil) [3, 8, 21] until definitively proven otherwise. The pupil is particularly prone to involvement from PComA because parasympathetic fibers to the iris pupillary sphincter muscle are in a peripheral and superomedial location in the third nerve as it passes near the PCom [22, 23]; however, 33% of all PCom aneurysmal partial third nerve palsies may have normal pupillary function at initial presentation, although the majority will develop pupillary involvement within 1 week [8]. Complete third nerve dysfunction is found immediately upon presentation in 20–36% of PComA [7, 8]. By 24 h and 1 week after presentation, 46% and 66% of third nerve palsies are complete, respectively. Fourteen percent remain partial and incomplete [7].

It is worth emphasizing that the term pupil-sparing complete third nerve palsy refers only to the situation in which the function of all third nerve-innervated structures except the pupil is 100% absent. It is a common misconception that recognition of pupil sparing in any third nerve palsy makes PComA less probable. This is absolutely untrue and clinical application of this misconception may result in SAH and death from rupture of an untreated aneurysm. A fair degree

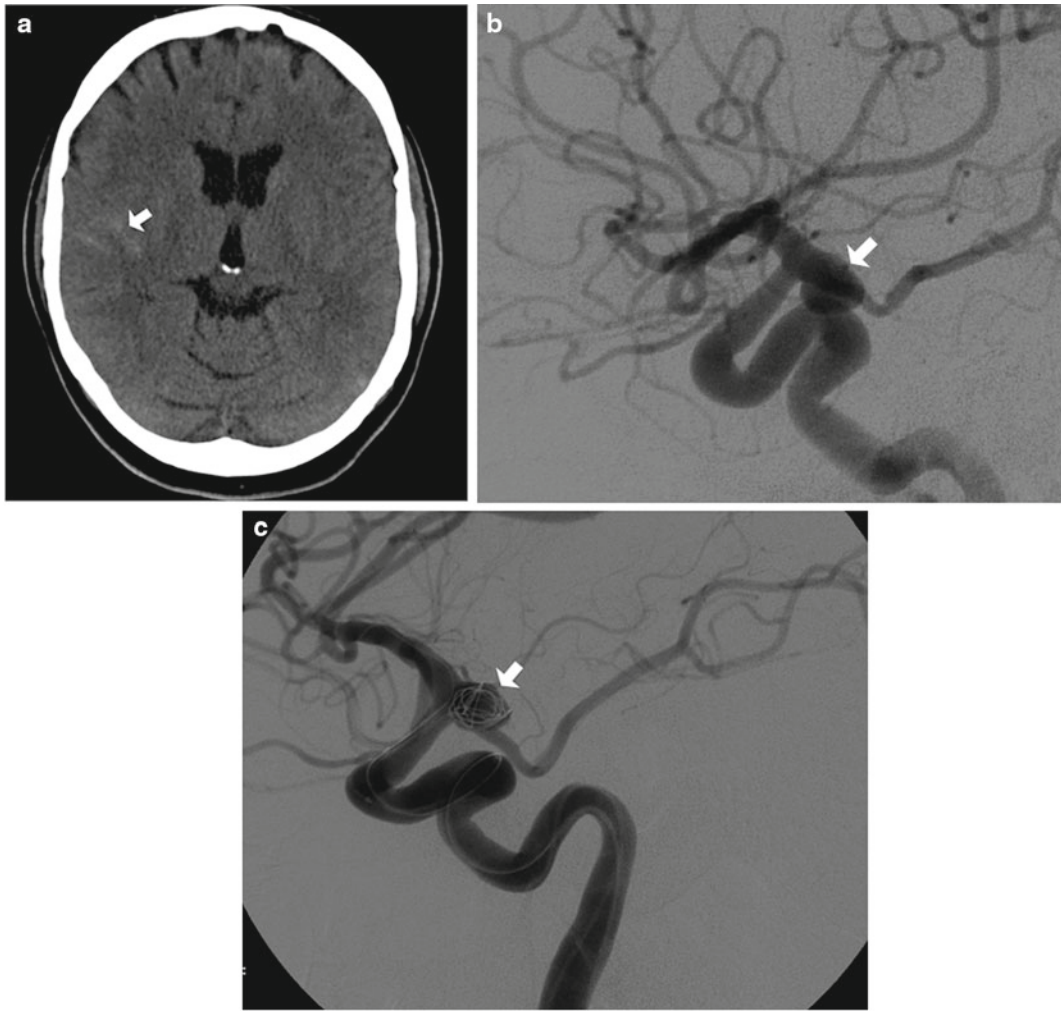

Fig. 6.7 (**a**) Head CT scan reveals focal subarachnoid hemorrhage in the right sylvian fissure (*white arrow*). Conventional cerebral angiogram demonstrates a 6.5×6×5.4-mm aneurysm at the junction of the right internal carotid artery and a fetal origin right posterior cerebral artery pretreatment (**b**, *white arrow*) and following endovascular coil embolization (**c**, *white arrow*). Images courtesy of Deborah Carson and Dr. Aman Patel

of confidence in a nonaneurysmal third nerve palsy etiology can only be attained when pupil sparing occurs in the setting of an otherwise complete third nerve palsy.

Spontaneous improvement in third nerve function may occur prior to aneurysm treatment and should not dissuade from full diagnostic evaluation for underlying PComA as the cause of a third nerve palsy [24]. Aberrant regeneration in the setting of third nerve dysfunction from a PComA usually develops following the acute third nerve palsy. Primary aberrant regeneration in the absence of an acute third nerve palsy is often due to a meningioma in the cavernous sinus or an intracavernous carotid artery aneurysm; however, it is also reported in the setting of PComA [25–27].

Third nerve dysfunction may occur in isolation due to an unruptured aneurysm or it may accompany SAH (Figs. 6.4, 6.7, and 6.8) with other neurologic symptoms and signs. Pain is present in over 60% of patients with an ipsilateral third nerve palsy due to PComA, even in the absence of SAH, and may precede development

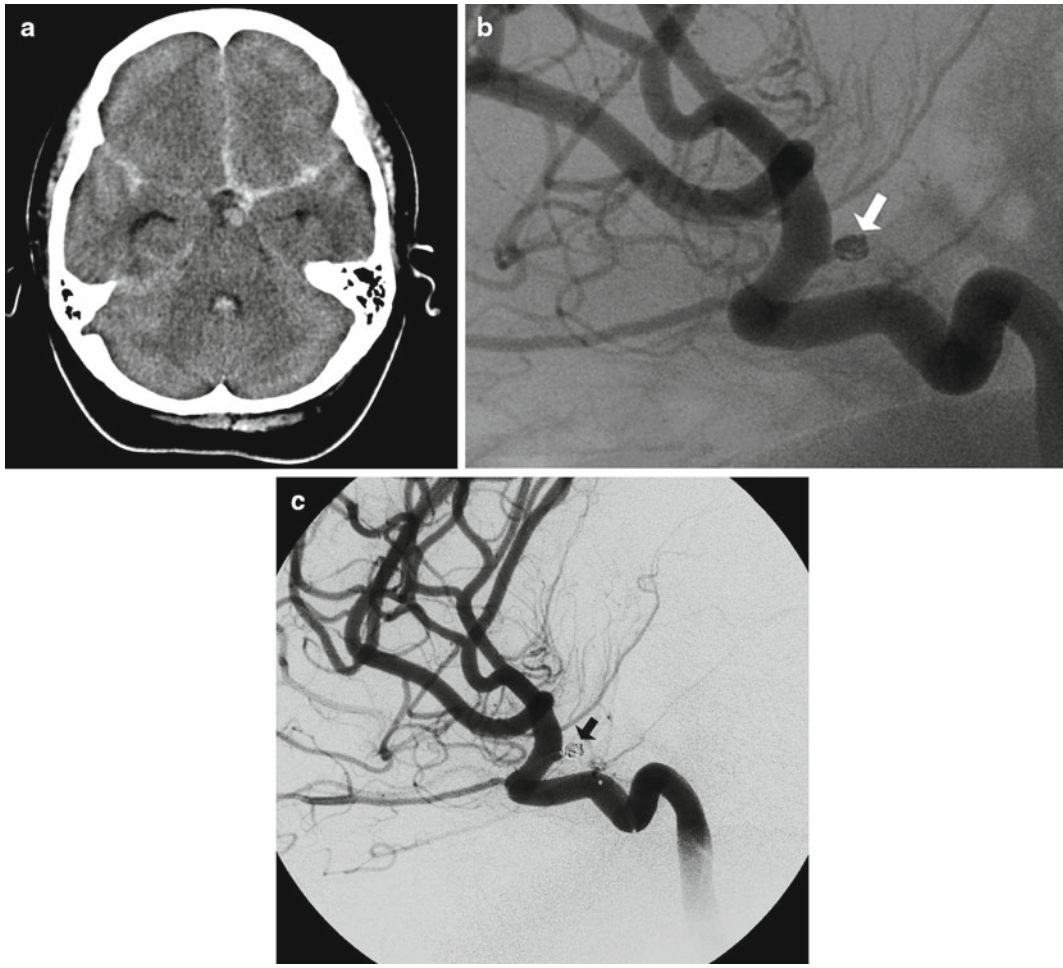

Fig. 6.8 (**a**) Head CT scan reveals subarachnoid hemorrhage. Conventional angiogram demonstrates a 3×2×2.8-mm aneurysm at the junction of the left internal carotid and posterior communicating arteries pretreatment (**b**, *white arrow*) and following endovascular coil embolization (**c**, *black arrow*). Compare the more extensive hemorrhage caused by this small aneurysm with the small amount of hemorrhage caused by the larger aneurysm in Fig. 6.7. Images courtesy of Deborah Carson and Dr. Aman Patel

of ptosis or diplopia by up to 2 weeks [7, 21]. The location of the pain is generally ipsilateral and periocular or retrobulbar and is thought to be due to involvement of sensory afferent fibers from the ophthalmic division of the fifth nerve that travel in the periphery of the third nerve [28]. Pain in this location accompanying a third nerve palsy, however, is not specific to PComA. It is also common in microvascular third nerve palsies [29]. The absence of pain does not exclude PComA as the cause of a third nerve palsy.

While PComA are, by far, the most common aneurysmal cause of third nerve palsies, any saccular or cerebrospinal fluid cisternal aneurysm is a neurologic emergency and third nerve palsy occurs occasionally from aneurysms in other locations, such as the basilar tip or anterior choroidal artery [21, 30, 31]. Rarely, SAH and third nerve palsy occur in the absence of an identified aneurysm. In this setting, an aneurysm may or may not be found upon repeat diagnostic evaluation [32, 33].

Brainstem Stroke

Ischemic and hemorrhagic midbrain stroke may cause unilateral or bilateral third nerve palsies due to involvement of the third nerve fascicle [34, 35]. Inferior and superior divisional partial third nerve

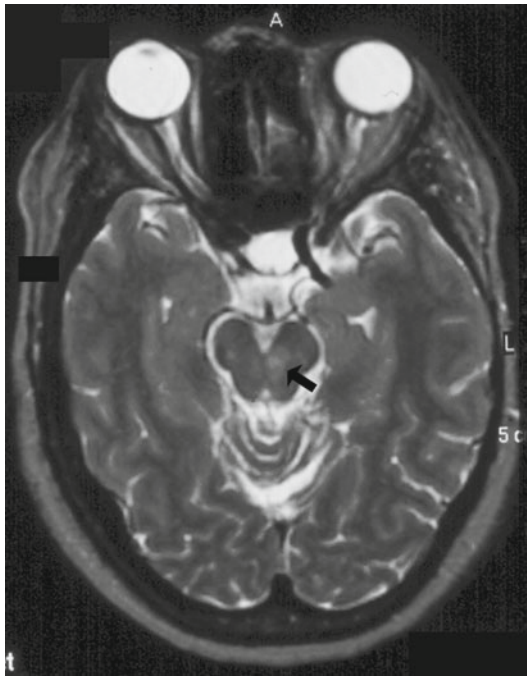

Fig. 6.9 T2-weighted axial brain MRI reveals increased T2 signal in the left ventral midbrain in a patient with ischemic Weber's syndrome with right hemiparesis and a left third nerve palsy

palsies (see above subsection "General Clinical Appearance" in this section) are reported, as are paresis of a single muscle and isolated mydriasis and ptosis in the absence of ocular motility deficits [17, 36–38]. Although isolated third nerve dysfunction has been reported, it is exceedingly rare and accompanying neurological signs are typically present. The following named brainstem syndromes occur most commonly with stroke. Current syndromic descriptions vary somewhat from the original descriptions [39]. All include an ipsilesional third nerve palsy in combination with contralesional ataxia (Claude's syndrome, superior cerebellar peduncle involvement), ipsilesional ataxia (Nothnagel's syndrome, superior cerebellar peduncle involvement), contralesional hemiparesis (Weber's syndrome, cerebral peduncle involvement) (Fig. 6.9), or contralesional chorea or tremor (Benedikt's syndrome, red nucleus involvement). Details regarding the clinical appearance of the third nerve palsy in these syndromes are few, but in Claude's syndrome, pupil-sparing partial third nerve dysfunction with predominant medial rectus involvement may be most common [40].

Third nerve palsies may also occur in combination with vertical supranuclear gaze palsies, as the midbrain is the location of the rostral interstitial medial longitudinal fasciculus and interstitial nucleus of Cajal, structures responsible for vertical gaze control. Third nerve dysfunction occurs in 35% of infarctions restricted to the midbrain [34]. Aberrant regeneration following an intra-axial cause of third nerve palsy is exceedingly rare, but is reported [41]. Demyelinating lesions may also affect the third nerve brainstem fascicle in isolation [4, 42, 43], or theoretically, in any of the above combinations.

Uncal Herniation

In the subarachnoid space, the third nerve passes in close proximity to the medial temporal lobe. Herniation of the temporal lobe uncus secondary to increased intracranial pressure may cause compression of the third nerve. This manifests clinically as sudden enlargement and poor reactivity of the pupil ipsilateral to the herniating uncus and is termed the "Hutchison's pupil."

Meningitis

Third nerve involvement in the interpeduncular fossa and subarachnoid space may occur secondary to infectious meningitis. Usually, the third nerve palsy will be persistent, but rarely may be transiently episodic. In the latter scenario, it may be due to an accompanying infectious vasculitis with transient ischemia to the nerve or to raised intracranial pressure [44, 45]. The patient will typically have accompanying signs suggesting meningitis, such as fever, nuchal rigidity, papilledema, or Kernig's and Brudzinski's signs.

Pituitary Apoplexy

Pituitary apoplexy is due to hemorrhage and necrosis within a preexisting pituitary adenoma. It may occur spontaneously or following a medical procedure, such as cardiac surgery (Fig. 6.10) [46–48]. Given the anatomic location of the third nerves within the dural walls of the cavernous sinuses directly lateral to the pituitary gland and sella, sudden lateral expansion of a pituitary adenoma from

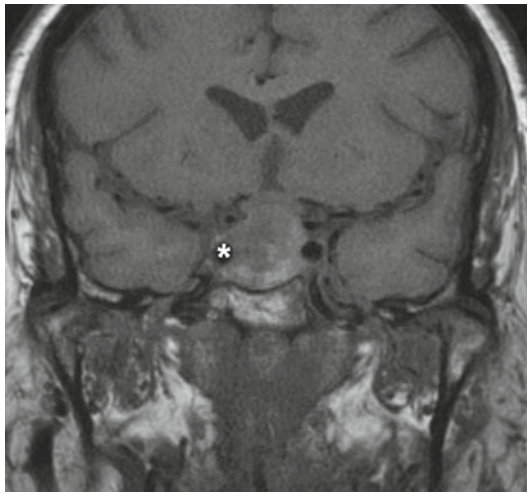

Fig. 6.10 Coronal T1-weighted noncontrasted brain MRI showing a pituitary adenoma in a 62-year-old patient who developed a right third nerve palsy, right optic neuropathy, and a bitemporal hemianopia with severe headache acutely following cardiac stent placement. Note the heterogenous signal characteristics within the adenoma, suggestive of hemorrhage and/or necrosis within a preexisting tumor. Also note the predominant lateral expansion of the mass toward the right (*asterisk* is placed within the right internal carotid flow void within the cavernous sinus), which explains the predominant right-sided presentation

apoplexy often leads to unilateral or bilateral third nerve palsies [49]. They may occur as an isolated sign [50, 51] (often associated with severe headache), but often are also accompanied by severe vision loss due to intracranial optic nerve and chiasmal compression via upward expansion of the pituitary mass. This condition is a true medical emergency not only because of the possibility of permanent vision loss if the optic apparatus is not quickly decompressed, but also because of its propensity to lead to Addisonian crisis.

Fungal Sinus Disease

Fungal sinus disease from aspergillosis or mucormycosis may spread to the orbital apex or cavernous sinus and cause third nerve dysfunction, often accompanied by dysfunction of neighboring structures. In the orbital apex, structures include the optic nerve, first division of the fifth nerve (trigeminal, CN V), fourth nerve (trochlear, CN IV), and sixth nerve (abducens, CN VI). In the cavernous sinus, structures include the first and second divisions of the fifth nerve, fourth nerve, and sixth nerve. With orbital apex involvement, proptosis and conjunctival injection and swelling may also be present. This diagnosis should be particularly suspected in patients with diabetes and in those who are immunosuppressed.

Giant Cell Arteritis

Ocular motor presentations of giant cell arteritis are uncommon, but are important to identify due to the high risk of bilateral blindness from ischemic optic neuropathies if left undiagnosed. Third nerve palsies are reported both in isolation and with simultaneous ischemic optic neuropathy [52, 53]. Any patient over the age of 70 with an acute-onset third nerve palsy should at least be questioned about typical giant cell arteritis symptoms of fatigue, jaw claudication, and scalp tenderness.

Sixth Nerve

General Clinical Appearance

A sixth nerve palsy results in impaired ipsilateral abduction of the eye and deviation of the eyes toward one another (esotropia). Binocular horizontal diplopia and the esotropia are worse with gaze in the direction of impaired abduction.

Brainstem Stroke

Ischemic and hemorrhagic pontine stroke may cause unilateral or bilateral sixth nerve palsies due to involvement of the sixth nerve fascicle. Although isolated sixth nerve dysfunction is reported [54, 55], accompanying neurological signs are often present. The following named brainstem syndromes occur most commonly with stroke. All include an ipsilesional sixth nerve palsy in combination with contralesional ataxia and ipsilesional facial weakness, Horner's syndrome, deafness, and loss of facial sensation and taste (Foville's syndrome); contralesional hemiparesis and ipsilesional facial weakness (Millard-Gubler's syndrome); or contralateral hemiparesis (Raymond's syndrome). Demyelinating lesions may also affect the sixth nerve fascicle in isolation or, theoretically, in any of the above combinations [56].

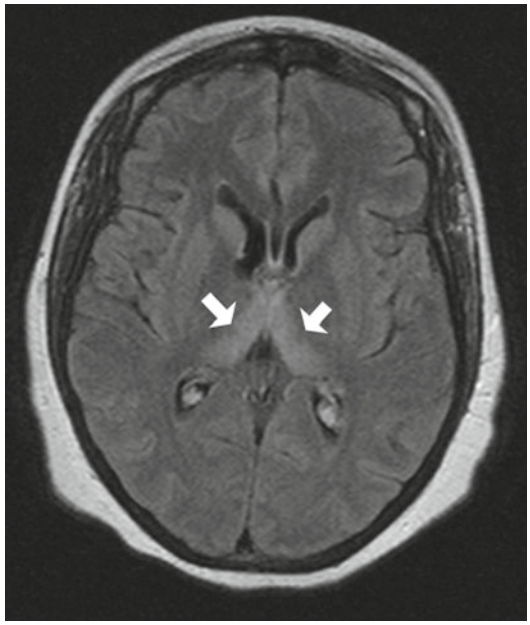

Fig. 6.11 Axial T2-weighted FLAIR brain MRI in a patient with Wernicke's encephalopathy demonstrating increased T2 signal in the medial thalami surrounding the third ventricle

Wernicke's Encephalopathy

The classic triad of Wernicke's encephalopathy is confusion, ophthalmoplegia, and ataxia. Horizontal gaze dysfunction, including sixth nerve palsy, is a common clinical finding in Wernicke's encephalopathy. Nystagmus is the only ocular motor feature that occurs with a higher frequency than sixth nerve palsy and the majority of patients exhibit both nystagmus and unilateral or bilateral sixth nerve palsies [57]. The accompanying nystagmus is generally gaze-evoked nystagmus, but may also be upbeat nystagmus. Characteristic MRI findings include increased T2 signal in the dorsal midbrain and medial thalami surrounding the third ventricle (Fig. 6.11). Improvement in sixth nerve dysfunction often begins within hours to days of treatment with thiamine.

Meningitis and Alterations in Intracranial Pressure

Sixth nerve involvement in the subarachnoid space may occur secondary to infectious or neoplastic meningitis, either from direct involvement of the nerve or secondary to raised intracranial pressure. The sixth nerves are particularly prone to dysfunction from alterations in intracranial pressure, including raised intracranial pressure due to cerebral vein thrombosis (Fig. 6.12) or idiopathic intracranial hypertension and spontaneous intracranial hypotension [58]. It was historically suggested that the sixth nerve was affected by alterations in intracranial pressure because of its long intracranial course; however it is shorter than the fourth nerve (trochlear nerve, CN IV), which is not prone to such injury. Rather, it is likely the tethering of the sixth nerve to the dura at its point of entry to Dorello's canal (see above section on "Pathophysiology and Anatomy of the Sixth Nerve") that leads to stretching and distortion of the nerve with alterations in intracranial pressure [59]. Within the subarachnoid space, the sixth nerve is also in close approximation with the clivus and the basilar and vertebral arteries and may be affected by neoplastic clivus disease or compression by an aneurysm [60].

Pituitary Apoplexy

Sixth nerve dysfunction is less commonly due to pituitary apoplexy than is third nerve dysfunction (see above section on "Clinical Appearance of Third Nerve Palsy") [49]. When it does occur, it tends to occur with simultaneous third nerve involvement. A single case of an isolated sixth nerve palsy as the presentation of pituitary apoplexy resulting in death is, however, reported [61].

Fungal Sinus Disease

A sixth nerve palsy may result from orbital apex or cavernous sinus extension of fungal sinus disease (see above section on "Clinical Appearance of Third Nerve Palsy" for more details about fungal sinus disease).

Giant Cell Arteritis

Sixth nerve palsies are reported in giant cell arteritis [62] (see above section on "Clinical Appearance of Third Nerve Palsy" for more details about giant cell arteritis).

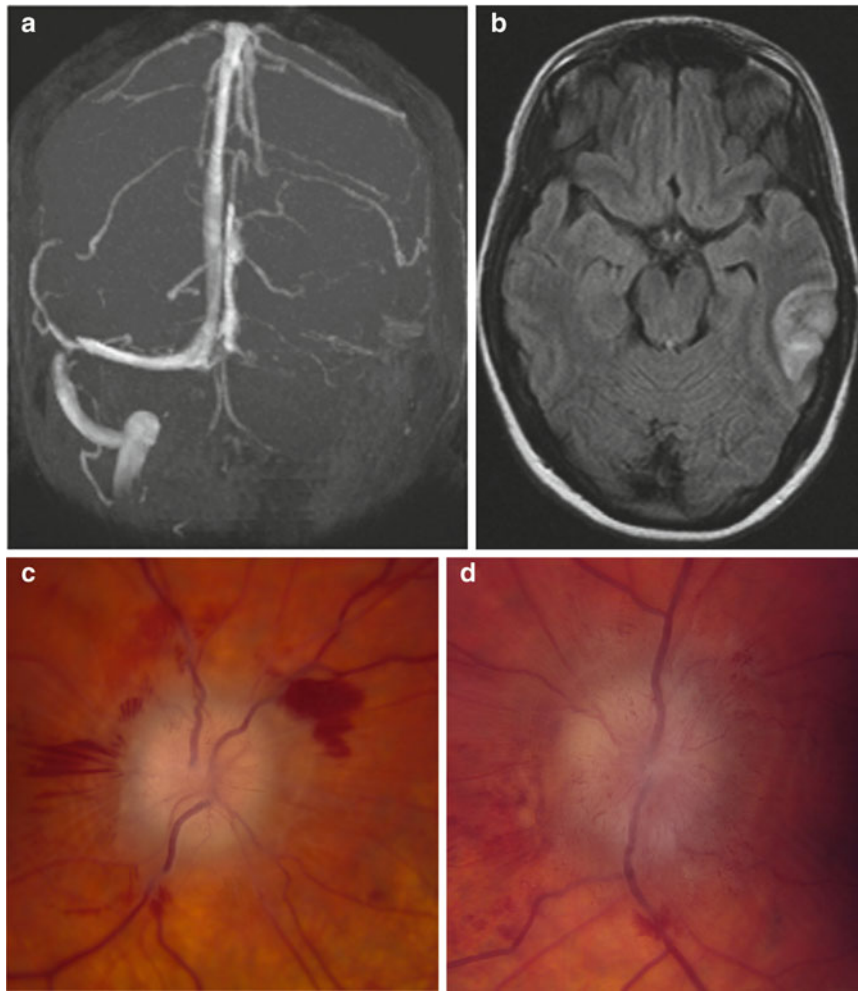

Fig. 6.12 (**a**) Magnetic resonance venogram demonstrating acute venous sinus thrombosis with lack of signal in the left transverse and sigmoid sinuses. (**b**) Axial T2-weighted FLAIR brain MRI reveals a left temporal lobe venous infarction. The patient presented with severe headaches, binocular horizontal diplopia due to bilateral sixth nerve palsies, and florid bilateral papilledema (**c**—right eye, **d**—left eye)

Diagnosis

Third Nerve

Emergent neuroimaging to evaluate for PComA is indicated in all third nerve palsies, with the sole exception of a pupil-sparing third nerve palsy that is otherwise complete, meaning complete ptosis and the complete absence of function of inferior, superior, and medial recti and the inferior oblique. Pupil sparing in this setting must also be complete, with no pupillary enlargement and a reaction to light that is equal in amplitude to the pupillary light reaction in the unaffected eye. The argument can be made, however, that every patient with a third nerve palsy should undergo neuroimaging regardless of pupillary status, as rare cases of PComA causing third nerve palsy without pupillary involvement are reported [3, 21, 63].

In the past, "gold standard" conventional intracranial angiography was the only means of accurate assessment for the presence of PComA.

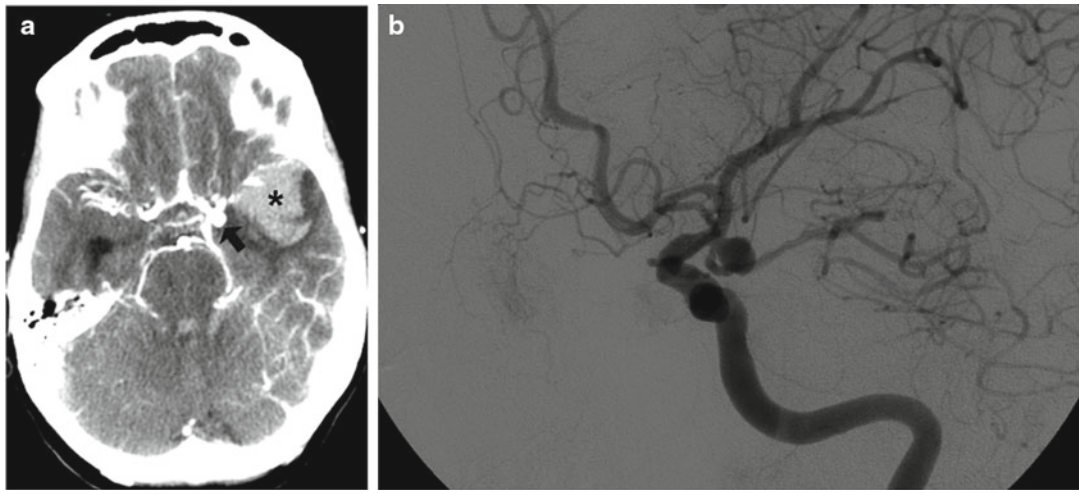

Fig. 6.13 (**a**) CT angiogram demonstrating a left temporal intraparenchymal hemorrhage (*asterisk*) and a 5×7-mm left posterior communicating artery aneurysm. (**b**) Conventional angiogram demonstrates the aneurysm pre-treatment. Images courtesy of Deborah Carson and Dr. Aman Patel

The 1–2% stroke risk accompanying angiography led many to conclude that patients over the age of 50 with a pupil-sparing third nerve palsy should not undergo conventional angiography, as the risk outweighed the likelihood of diagnosing an aneurysm [64, 65]. Magnetic resonance angiography (MRA) and CT angiography (CTA) (Fig. 6.13) have largely supplanted conventional cerebral angiography as the preferred diagnostic tests for aneurysm detection; however, neither of these techniques is 100% sensitive across studies, so conventional angiography remains the gold standard and should be performed when clinical suspicion for an aneurysm is high and noninvasive imaging techniques are normal [66]. The sensitivity of MRA and CTA is significantly affected by technical quality and experience level of the radiologist. Aneurysms large enough to cause third nerve palsies are usually at least 4–5 mm, but are often less than 10 mm [21]. The sensitivity of MRA for aneurysms 5 mm or greater is in the 90–97% range, but drops to the 60–80% range for aneurysms less than 5 mm; for CTA, the sensitivity for aneurysm detection is in the 90–100% range, but drops to 79% for aneurysms less than 5 mm [67–74]. A technically adequate and correctly interpreted MRA will miss 1.5% of third nerve palsy-causing PComA that will rupture in the next 8 years, if left untreated [71]. CT angiography, even if performed with a brain CT scan, will fail to detect most nonaneurysmal causes of third nerve palsy. If aneurysm is effectively excluded by CTA and/or conventional angiography, gadolinium-enhanced brain MRI may still be necessary to seek an alternative etiology.

Microvascular

Although microvascular third nerve palsies are not neurological emergencies and do not warrant neuroimaging if the diagnosis is firmly established, they are among the most frequent cause of third nerve palsies and must be distinguished from other emergent causes of third nerve dysfunction. An isolated, painful, pupil-sparing third nerve palsy in an older patient with vascular risk factors is likely to be due to microvascular ischemia to the nerve; however, as discussed in the above section on "Clinical Features" of third nerve palsy due to PComA, a large percentage of third nerve palsies from PComA progress over several days to weeks, so one can only be relatively confident in a microvascular diagnosis if third nerve dysfunction in a pupil-sparing third nerve palsy is otherwise complete. As stated above, emergent neuroimaging to evaluate for

PComA is indicated in all third nerve palsies, with the sole exception of a pupil-sparing third nerve palsy that is otherwise complete, meaning complete ptosis and the complete absence of function of inferior, superior, and medial recti and the inferior oblique. Pupil sparing in this setting must also be complete, with no pupillary enlargement and a reaction to light that is equal in amplitude to the pupillary light reaction in the unaffected eye.

Relative pupil involvement with an average of 0.8 mm of anisocoria may be seen in up to one-third of patients with microvascular third nerve ischemia; however, the pupil generally remains reactive [75]. Relative pupil involvement is also commonly seen with compressive mass lesions [76]. Rarely, up to 2 mm of anisocoria is seen with microvascular ischemia [77]. Spontaneous resolution of a microvascular cranial mononeuropathy occurs over 8–12 weeks. In the absence of complete, spontaneous resolution, diagnostic testing to include brain MRI with gadolinium and lumbar puncture may be indicated to exclude an alternative etiology. Development of aberrant regeneration following a presumed microvascular etiology should also immediately prompt neuroimaging, as aberrant regeneration does not generally occur in this setting.

Head Trauma

A third nerve palsy caused by closed mechanical head trauma may or may not be a neurological emergency. A third nerve palsy due to raised intracranial pressure with uncal herniation from intracranial (epidural, subdural, or intraparenchymal) hemorrhage is a neurological emergency. Direct traumatic mechanical injury to the third nerve may not be. When third nerve dysfunction is found in the setting of head injury, a previously asymptomatic underlying lesion, such as PComA or skull-based intracranial tumor [78, 79], should be sought unless the head trauma was extremely severe, usually with loss of consciousness and basilar skull fracture [80, 81]. Onset of a third nerve palsy following trivial head injury suggests that the nerve is stretched over or compressed by an underlying lesion, although cases lacking identification of an underlying lesion are reported [82–84].

Sixth Nerve

The need for emergent neuroimaging in acute isolated sixth nerve palsy is controversial, especially in patients over the age of 50 with vascular risk factors [77, 85].

Microvascular

Although microvascular sixth nerve palsies are not neurological emergencies and do not warrant neuroimaging if the diagnosis is firmly established, they are among the most frequent cause of sixth nerve palsies and must be distinguished from other emergent causes of sixth nerve dysfunction. An isolated, painful sixth nerve palsy in an older patient with vascular risk factors is likely to be due to microvascular ischemia to the nerve. Compared with third nerve palsies where a PComA must not be missed, the decision if and when to perform neuroimaging in the scenario of a probable microvascular isolated sixth nerve palsy is generally considered less emergent. Spontaneous resolution of a microvascular cranial mononeuropathy occurs over 8–12 weeks. In the absence of complete, spontaneous resolution, neuroimaging is essential.

Head Trauma

A sixth nerve palsy caused by closed mechanical head trauma may or may not be a neurological emergency. A sixth nerve palsy due to raised intracranial pressure from traumatic intracerebral (epidural, subdural, or intraparenchymal) hemorrhage is a neurological emergency. Direct traumatic mechanical injury to the sixth nerve is not. Such mechanical injury may be caused by even minor head trauma without loss of consciousness [81].

Treatment and Prognosis

Third Nerve

Treatment for a third nerve palsy consists of treatment of the underlying etiology (aneurysm, stroke, fungal meningitis, or sinusitis, etc.), as well as treatment directed at alleviating binocular diplopia. When complete ptosis is present, the affected eye is essentially patched. Ptosis often

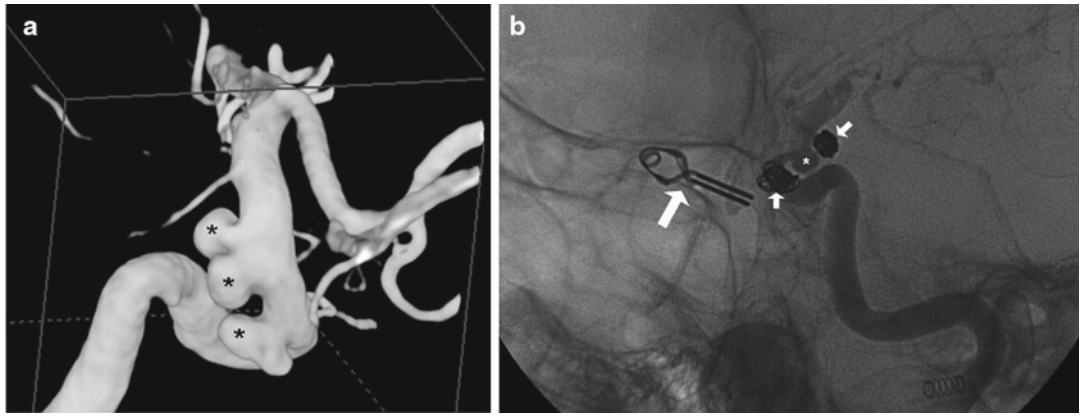

Fig. 6.14 (**a**) Three-dimensional conventional angiographic reconstructed image demonstrating three untreated aneurysms along the supraclinoid left internal carotid artery (*three black asterisks*). The most proximal is a superior hypophyseal artery aneurysm. The distal two are in the region of the posterior communicating artery. (**b**) Posttreatment angiogram demonstrating different treatment approaches. The proximal and distal left-sided aneurysms were treated with endovascular coil embolization (*two small white arrows*). The middle aneurysm (*white asterisk*) was ultimately treated by stent placement across its base due to catheter inaccessibility for coiling. The surgical clip used to treat a previously diagnosed right internal carotid artery aneurysm is also visible (*large white arrow*). Images courtesy of Deborah Carson and Dr. Aman Patel

resolves before ocular motor deficits and diplopia. Treatment may consist of patching one eye, placement of temporary Fresnel press-on prisms on the patient's glasses, and ultimately strabismus surgery if the deficits fail to improve and demonstrate stability for several months. Complete or partial recovery occurs in approximately 50% of all third nerve palsies [4].

With regard to intracranial aneurysms, the annual rupture rate is 0.05–2% [86]. A higher rate is associated with prior SAH, symptomatic presentation, posterior aneurysm location, and larger aneurysm size; however, even small, unruptured aneurysms presenting with third nerve palsy may rupture and lead to death before treatment occurs [21, 30, 86]. The true rupture risk for small aneurysms is ill-defined [87]. Treatment options include surgical clipping and neurointerventional endovascular coiling (Fig. 6.14). Rates of third nerve recovery after surgical clipping are fairly well documented, with overall complete third nerve recovery in 41–57% of all patients and some degree of recovery in 93% [21, 86]. Improved outcomes occur with earlier aneurysmal treatment [7, 21]. Sixty-four percent of patients who undergo surgical clipping within 2 weeks of symptom onset reach complete recovery, compared with only 14% when treatment is delayed beyond 30 days [86, 88]. Outcomes following endovascular coil embolization are less well defined, but most recover at least partially [89, 90]. The presence of complete third nerve dysfunction at presentation is a poor prognostic sign for posttreatment recovery [30, 91].

Sixth Nerve

Treatment for a sixth nerve palsy consists of treatment of the underlying etiology (stroke, fungal meningitis or sinusitis, raised intracranial pressure, etc.), as well as treatment directed at alleviating binocular diplopia. This may consist of patching one eye, placement of temporary Fresnel press-on prisms on the patient's glasses, and ultimately strabismus surgery if the deficits fail to improve and demonstrate stability for several months. Complete or partial recovery occurs in approximately 50% of all sixth nerve palsies [4].

Conclusion

Third and sixth nerve palsies, whether isolated or with accompanying neurological symptoms and signs, may represent true neurologic emergencies

with a high risk or morbidity and mortality if undiagnosed. A systematic and careful approach to each patient and a low threshold for neuroimaging are required to avoid common diagnostic pitfalls and misconceptions.

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Facial Nerve Palsy

7

James M. Gilchrist

Abstract

Facial neuropathy is the most common cranial neuropathy, due to its extensive course and multiple sites of potential injury. The causes of facial neuropathy are many, but 70% are diagnosed as Bell's palsy, an idiopathic syndrome but increasingly being associated with herpes simplex virus infection as the cause of the majority of cases. Ramsay Hunt syndrome (herpes zoster oticus) is the second most common cause. Facial neuropathy causes weakness of the muscles of facial expression on the ipsilateral side, and can be distinguished from a central, or upper motor neuron, caused by the involvement of forehead muscles. Taste, hearing, salivation, lacrimation, and sensation over the ipsilateral ear and the face may also be disturbed. Diagnosis can be confirmed by electrodiagnostic testing or MRI but is often not necessary. Treatment is directed at the underlying cause. In cases of Bell's palsy a short course of steroids has been shown effective, if started within 72 h of onset. Treatment with antiviral agents against herpes virus is probably best reserved for patients with severe or complete facial neuropathy or those with Ramsay Hunt syndrome.

Keywords

Antiviral agents • Bell's palsy • Herpes simplex • Herpes zoster • Lyme • Ramsay Hunt syndrome • Seventh cranial neuropathy • Steroids

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Introduction

The facial nerve, also known as the seventh cranial nerve, is the most commonly diagnosed cranial neuropathy. The reasons for this lie in its anatomy and its obviousness. The facial nerve has both an intracranial and an extracranial course, taking three significant bends along the way and traversing several potential points of difficulty (lateral pons, cerebellopontine cistern, the bony facial canal which it shares for part of the way with the acoustic nerve, the inner ear, the parotid gland). And facial nerve palsy is the absolute manifestation of being "in your face." The facial nerve provides innervation for muscles of facial expression, which is a primary mode of expressing emotion in humans and an important aspect of nonverbal communication, as well as a major aesthetic component of beauty. As such, we are especially attuned to facial movement and any asymmetry is immediately evident and upsetting. Patients do not sit at home and wait out a new facial palsy. They set out for the emergency room soon after onset and with considerable anxiety.

Epidemiology

Facial neuropathy is a common neurologic syndrome, and 70% will be diagnosed as Bell's palsy [1]. The annual incidence of Bell's palsy is 25 per 100,000 [2] with a lifetime risk of 1 in 60–70 [3]. Males and females are affected equally and the frequency per decade of life is remarkably similar between age 10 and over 70 years of age [2]. There is no preference between right and left sides, though bilateral involvement is rare, at 0.3–2% [4].

Ramsay Hunt syndrome is the second most common cause of facial neuropathy and can occur in children (16.7% of unilateral facial palsies) and adults (18.1% of facial palsies) with nearly equal frequency, though less so in children under the age of 6 [5]. Zoster sine herpete looks to be especially common in children between 6 and 15 years of age and may account for over a third of all facial neuropathies in that age group [6, 7].

Pathophysiology and Pathogenesis

Facial nerve palsy cannot truly be understood without at least some knowledge of the anatomy of the seventh cranial nerve (Fig. 7.1). The motor root of the facial nerve arises in the facial nucleus in the lateral pons. Fibers leaving the nucleus execute a loop (the internal genu of the facial nerve) around the nucleus of the abducens nerve, traveling medially from below to above the sixth nerve nucleus before exiting at the pontomedullary junction. The motor root then traverses the cerebellopontine cistern to enter the internal acoustic canal. The sensory root of the facial nerve is separate from the motor root between the brainstem and the internal acoustic canal and is often called the nervus intermedius. Within the nervus intermedius are sensory fibers which end in the spinal nucleus of cranial nerve V, and parasympathetic fibers.

In the internal acoustic canal, the now-whole facial nerve is accompanied by the eighth cranial nerve. The nerves travel to the meatal foramen ("porous acusticus"), which is divided into bony compartments, to then enter the facial canal, also called the fallopian canal. The meatus is the narrowest portion of the entire facial canal, less than 0.7 mm [8]. The facial nerve then enters the labyrinthine portion of the facial canal, so called because it is close to the superior semicircular canal. The labyrinthine canal ends at the geniculate ganglion, where the cell bodies of the sensory and parasympathetic neurons are located. The greater petrosal nerve branches off at the geniculate ganglion to head to the sphenopalatine and pterygopalatine ganglia, from whence it supplies the lacrimal gland with parasympathetic innervation. From the geniculate ganglion, the facial canal takes its first external genu, and is called the tympanic segment. The nerve to the stapedius muscle branches off within the tympanic canal. The tympanic segment ends as the facial canal makes its second external bend, this time at a 90° angle. The final intracranial part of the facial canal is called the mastoid segment and proceeds in a vertical descent to the stylomastoid foramen where the facial nerve becomes extracranial.

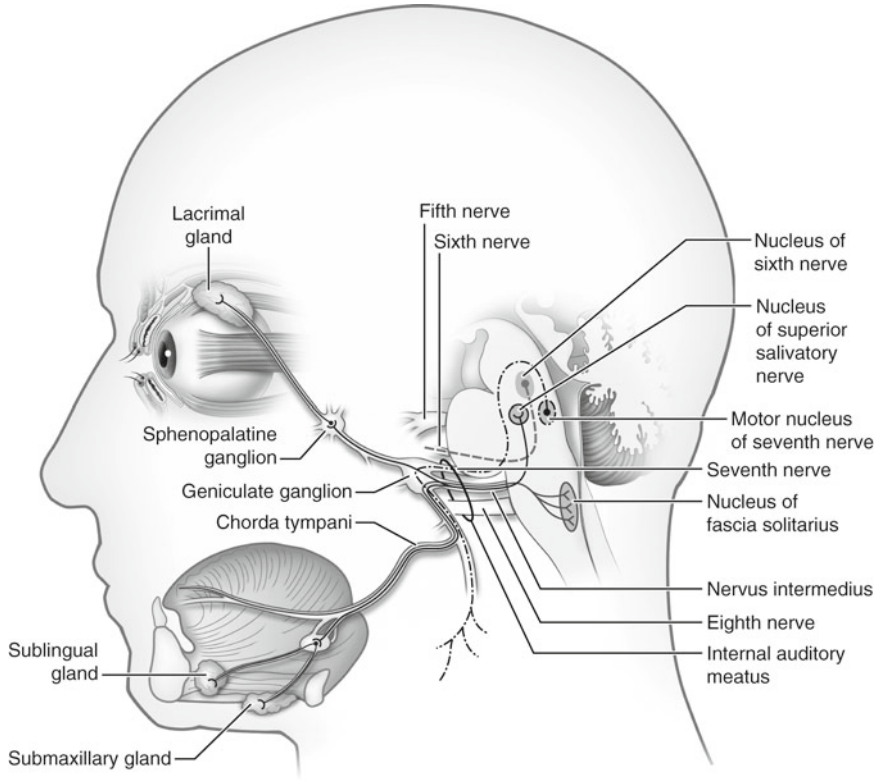

Fig. 7.1 Anatomy of the seventh cranial nerve

The chorda tympani branches off in the mastoid segment and then enters the tympanic cavity before joining the lingual nerve. It sends preganglionic parasympathetic fibers to the sublingual and submaxillary glands. The chorda tympani also conveys taste from the anterior two-thirds of the tongue. Once the facial nerve is extracranial, it divides into the posterior auricular branch which supplies sensation to the auricle and pinna of the ear, although it also has motor fibers. Other terminal branches control muscles of facial expression, as well as branches to the digastric and stylohyoid muscles.

The potential causes of facial neuropathy are protean (Table 7.1), as are the related pathophysiologies. There is mounting evidence that Bell's palsy is associated with herpes simplex (HSV) infection. McCormick first postulated a connection with HSV infection in 1972 [9], and several lines of evidence support that up to 79% of Bell's palsy is caused by reactivated HSV infection in the geniculate ganglion [10]. Increased rates of HSV genome fragments by PCR were seen in the saliva of patients with Bell's palsy [11], and PCR also identified such fragments in human geniculate ganglia at autopsy [12, 13]. Murakami found active HSV sequences in the endoneurial fluid of the facial nerve in patients with Bell's palsy [14], and facial neuropathy was induced in animals by reactivating HSV [15–18]. Reactivation of the HSV virus presumably causes inflammation of the facial nerve in the facial canal, initially causing demyelination, but if severe, causing axonal damage and Wallerian degeneration distal to the lesion [19].

Ramsay Hunt first described the condition which bears his name in 1907 [20]. Ramsay Hunt syndrome is defined as a peripheral facial neuropathy accompanied by an erythematous vesicular rash of the ear (herpes zoster oticus) or mouth [20]. The infection involves the contiguous facial nerve in the tympanic segment, leading, as in

Table 7.1 Causes of unilateral seventh cranial neuropathy

Relatively common
Bell's palsy (idiopathic)
Herpes simplex virus
Ramsay-Hunt syndrome (herpes zoster)
Lyme
Zoster sine herpete
Trauma
Diabetes mellitus
Pregnancy
Guillain–Barré syndrome
Sarcoid
Neoplastic meningitis
Pontine infarct
Pontine hemorrhage
Multiple sclerosis
Brainstem tumor
Facial neuropathy from forceps/birth trauma
Acoustic neuroma
Relatively less common
Pontine
Encephalitis
Abscess
Congenital/postnatal
Mobius syndrome
Hemicranial microsomia
Congenital lower lip paralysis
Kawasaki disease
Albers-Schoenberg (osteopetrosis)
Infantile hypercalcemia
Cardiofacial syndrome
Tumor
Meningioma
Cholesteatoma
Metastatic
Neurinoma
Parotid tumor
Meningitis
Infectious
Bacterial
Fungal
Tuberculous
Syphilis
Parasitic (trichinosis, neurocystercercosis)
Inflammatory
Leukemia (children)
Infections
HIV seroconversion
Osteomyelitis of skull base
Otogenic infections
Parotitis/abscess
Mastoiditis
Leprosy
Poliomyelitis
Mycoplasma
Influenza
Miscellaneous
Benign intracranial hypertension
Melkersson–Rosenthal
Amyloidosis
Wegener's granulomatosis
Polyarteritis
Sjogren's syndrome
HTLV-1
Hereditary neuropathy with pressure palsies (HNPP)
Familial Bell's
CIDP
Charcot-Marie-Tooth
Histiocytosis X
Interferon therapy
Sclerosteosis
Ethylene glycol intoxication
Wernicke–Korsakov syndrome
Stevens-Johnson syndrome

Bell's palsy, to inflammation, edema, demyelination, and potentially, axonal damage. Ramsay Hunt syndrome can be seen in the absence of a rash (zoster sine herpete) when accompanied by either a fourfold rise in varicella zoster virus (VZV) antibody or detection of VZV DNA [20]. This may occur in anywhere from 2.4% to 19% [5, 21] of patients who otherwise might have been thought to have Bell's palsy.

The cause of Lyme facial neuropathy is likely not from meningitis. Halperin examined the CSF of 31 patients with Lyme facial neuropathy [22]. Only 11 had CSF pleocytosis, and nine had elevated protein concentration, and he suggested that meningitis might occur concomitantly with facial neuropathy but not as a cause of facial neuropathy [22].

Clinical Features

Facial neuropathies can affect either sex and occur at any age [2]. Facial neuropathies are nearly always unilateral [4], with only 1–2%

being bilateral. The most obvious finding on examination is facial paresis or paralysis ipsilateral to the neuropathy, involving all muscles of facial expression, although to potentially varying degrees. This is in contradistinction to facial weakness from a lesion above the level of the pontine facial nucleus (such as from a stroke), which will cause weakness of contralateral lower facial muscles only, sparing the frontalis muscle. The facial nucleus receives cortical innervation for muscles of the upper face from both cerebral hemispheres, but only from the contralateral cerebral hemispheres for lower facial muscles.

Facial neuropathies proximal to or at the level of the geniculate ganglion will also cause hyperacusis due to paralysis of the stapedius muscle, but there will not be any hearing loss from an isolated facial neuropathy. In addition, salivation and lacrimation will be hindered or lost altogether due to damage to parasympathetic fibers. Lesions at or proximal to the second external genu (i.e., in the tympanic segment of the facial canal) will result in dysgeusia and xerostomia from damage to the chorda tympani. Sensation over the ipsilateral ear lobe will be affected in any facial neuropathy proximal to the stylomastoid foramen. Subjective and/or objective numbness over the paretic portions of the face is also not uncommon [2]. This is presumed due to connections between the maxillary branch of the trigeminal nerve and the sphenopalatine ganglion [23]. Pain early in the course is present in a significant minority of patients with Bell's palsy [2] and a high proportion of patients with Ramsay-Hunt disease [20]. As the orbicularis oculi will be weak, inhibiting complete eye closure, protection of the cornea is important, especially at night when the patient is asleep. Eye lubrication and taping the eye shut should be instituted immediately in any patient with incomplete eye closure. Patching the eye alone is not appropriate, especially with gauze, as that will wick away lacrimation, and hasten corneal injury. Other cranial nerve abnormalities, such as hearing loss, tinnitus, dysphagia, dysarthria, and diplopia, often accompany secondary causes of facial neuropathy and require further evaluation.

In Ramsay Hunt syndrome, facial weakness reaches maximum by 1 week after onset with severe to complete paralysis in 52% of adults and 44% of children [5]. Age over 50 years, complete paralysis and lack of nerve excitability are poor prognostic factors [24]. Between 80% and 85% will have a good recovery [5]. Unlike Bell's palsy, other cranial neuropathies (VIII, IX, or X) are frequent, with up to 53% of adults suffering hearing loss, which did not improve in 38% [5]. Tinnitus and vertigo are also common [5].

Cranial neuropathies occur in 5–10% of patients with Lyme disease and 80% are facial neuropathies [25]. Lyme disease is a relatively frequent cause of bilateral facial neuropathy. Unilateral or bilateral facial palsies are the most frequent neuropathic manifestation, accounting for 50% of patients with neurologic involvement [26]. Residual symptoms of Lyme-associated facial neuropathy are uncommon, with complete or near-complete recovery in over 90%, even without treatment [22, 27]. Peripheral Lyme serologic testing is abnormal in 90% of patients at the time of facial neuropathy but can also become positive subsequently [22]. Western blots are usually negative, consistent with facial neuropathy being a very early manifestation of Lyme disease, and erythema migrans is also uncommon [22].

The time course of recovery from facial palsy is dependent on the type and degree of pathophysiologic lesion. A neurapraxic, or purely demyelinative, lesion will recover within days to weeks as the Schwann cell remyelinates the affected segment. More severe lesions resulting in axonal damage and distal Wallerian degeneration will take longer to recover function as nerve regeneration will be required. The regeneration may well be incomplete, resulting in the major sequelae of facial palsy, which are persistent paresis or paralysis, corneal injury secondary to incomplete eyelid closure, facial muscle contracture, and synkinesis [28]. Synkinesis is the phenomenon whereby the intended activation of one muscle will result in contraction of other muscles as well. This cocontraction may be due to either aberrant nerve fiber regeneration or to ephaptic transmission. Facial synkinesis can involve motor nerve fibers as well as fibers to the lacrimal and salivatory glands, resulting in the so-called crocodile tears phenomenon, in which gustatory salivation

causes tearing as well. Facial synkinesis is seen in the majority of patients with Bell's palsy who have evidence of axonopathy [28].

Diagnosis

The diagnosis of facial palsy does not require sophisticated testing and should be possible using bedside acumen. The most common diagnostic question for acute unilateral facial weakness is between facial neuropathy and a stroke, and this should not be clinically difficult. Upper motor neuron, or "central," facial weakness spares the forehead, does not cause hyperacusis, dysgeusia or pain, and usually involves symptoms and signs beyond the face. Examination of the ear, tympanic membrane, and mouth for vesicles is important and an ELISA screen for Lyme disease is essential in any area endemic for the *Borrelia burgdorferi*-bearing deer tick, *Ixodes scapularis*. Lumbar puncture is not routinely indicated unless there are complicating factors, such as multiple cranial neuropathies, significant meningismus, or other neurologic signs or symptoms implying involvement beyond the facial nerve.

The electrodiagnostic methods most commonly used to study the facial nerve are direct facial motor nerve conduction studies (electroneurography). Most patients referred to the EMG laboratory because of a facial paresis are sent for a prognosis, which is directly related to whether the facial nerve lesion is demyelinative or axonopathic. Electrodiagnostic studies are quite useful for making that determination but are limited because Wallerian degeneration of motor nerve fibers takes 5–8 days after axonal injury and NCSs will be of little prognostic value before that time [29].

Amplitude of the direct motor nerve evoked response 5–7 days after onset is probably the best available method [30–32]. When the CMAP amplitude is less than 10% of that on the healthy side, maximum recovery will be delayed 6–12 months and function will be moderately or severely limited. If the amplitude is 10–30% of the healthy side, recovery may take 2–8 months with mild to moderate residua. If the CMAP amplitude is >30% of normal, full-complete recovery can be expected at 2 months after onset [33].

Latency of the direct facial motor nerve stimulation is not as useful as amplitude measurement [34]. When done 5–7 days after onset, three types of evoked responses are found: normal, which virtually assures patients of a complete recovery without aberrant recovery; prolonged latency compared with the opposite side, with frequent good recovery but some chance of synkinesis; and no response, with high incidence of synkinesis and some patients with no recovery.

The blink reflex is the electrical correlate of the bedside corneal reflex [32]. The blink reflex differs from direct facial nerve study in that it examines the trigeminal nerve and the pons in addition to the facial nerve, and assesses proximal segments of the facial nerve inaccessible to the direct stimulation technique. Facial motor synkinesis can be assessed by expanding the set up for the blink reflex to also include recording electrodes over the orbicularis oris or other facial muscles [32]. The blink reflex as a prognostic method has not been particularly helpful in that it offers little beyond direct facial nerve studies and is limited by the same time constraints.

At this time there is no electrodiagnostic technique which reliably predicts prognosis in Bell's palsy within the first 24–48 h after onset. CMAP amplitude comparing side-to-side difference at day 5–7 after onset appears to be the most reliable parameter for ultimate prognosis [30, 32].

MRI with gadolinium enhancement allows imaging of the abnormal facial nerve but is not usually indicated in isolated, unilateral facial neuropathy. A very high percentage of Bell's palsy patients will show enhancement, as will 50% of Ramsay Hunt disease patients [35]. Enhancement can also be seen in Lyme-related facial palsy. The only diagnostically reliable abnormality is enhancement in the distal intracanalicular and labyrinthine segments [36], but other than confirming the diagnosis, enhancement provides no indication of severity or prognosis [35, 37]. Enhancement can persist for weeks or months after resolution of the facial palsy. For patients suspected of secondary causes of facial neuropathy, MRI may be indicated to assess for

pontine lesions, cerebellopontine cistern and internal acoustic canal masses, and meningitis.

Differential Diagnosis

As discussed above, the primary initial differential is between facial neuropathy and a stroke. Once this has been clarified in favor of facial neuropathy, the differential is between Bell's palsy, an idiopathic facial neuropathy, and secondary causes of facial neuropathy (see Table 7.1). Bell's palsy accounts for up to 70% of facial neuropathy [1]. As mentioned above, clues to secondary causes include involvement of other cranial nerves (with the exception of mild subjective or objective sensory loss over the cheek), and signs or symptoms of other neurologic involvement. Concomitant medical conditions associated with facial neuropathy (see Table 7.1) would also be reasons to look beyond Bell's palsy. The most common secondary cause is Ramsay Hunt syndrome from herpes zoster oticus, which may account for up to 18% of facial neuropathies [5], and will be mistaken for Bell's palsy if the external auditory canal, mouth, and tongue are not examined for vesicles [20].

The presence of bilateral facial neuropathy, while uncommon, provides a further clue to etiology. Bell's palsy remains the most common cause [4], but Guillain-Barré and Miller Fisher syndromes need to be considered, as do HIV infection, meningitis, a variety of pontine pathologies, and Lyme disease [4].

Treatment

The pathophysiologic theory that Bell's palsy is caused by inflammation in the facial canal, presumably secondary to HSV reactivation, which leads to demyelination and, if severe, to axonal loss, has led to the hypothesis that steroids and/or antiviral agents will assist in the recovery from Bell's palsy and lead to lower long-term sequelae such as paralysis, paresis, and synkinesis.

Until recently, the assessment of whether steroids or antivirals, or both, were beneficial in Bell's palsy was hindered by few randomized trials with limited number of patients. In the latest Cochrane review of steroids in Bell's palsy, published in 2004, there were only four trials with a total of 179 patients [38]. No significant difference between steroids and nontreatment was found. Nearly the same conclusion was reached by the authors of a Cochrane review of antiviral agents in Bell's palsy [39]. They found only three randomized trials which met inclusion criteria, with a total of 246 patients. Benefit was again uncertain, as was harm.

Three recent studies and a meta-analysis have helped to clarify the picture, although controversy remains. In 2007, Hato et al. [40] published a prospective, randomized, multicenter, placebo-controlled trial of valacyclovir and prednisone versus placebo and prednisone. The valacyclovir dosage was 1,000 mg/day for 5 days, and prednisone was 60 mg/day for 5 days, 30 mg/day for 3 days, and 10 mg/day for 2 days. The overall results indicated 96.5% of patients treated with both valacyclovir and prednisone recovered versus 89.7% for those treated with placebo and prednisone, which was significant at $p<0.05$. But the largest difference was in those patients with complete palsy, and if complete and severe palsy were grouped together, the absolute rate of improvement increased to 9.1% (as versus 6.8% in the entire group) [40].

Also in 2007, Sullivan et al. [41] published a prospective, randomized, placebo-controlled trial of Bell's palsy within 3 days of onset. There were four groups, receiving either 10 days of prednisolone, acyclovir, both, or placebo. The prednisolone was dosed at 25 mg twice daily, and the acyclovir was 400 mg five times daily. They analyzed the final outcome of 496 patients. In patients receiving placebo, 64.7% recovered by 3 months and 85.2% by 9 months. For steroid versus no steroid, 83% improved at 3 months versus 63.6%, for an odds ratio of 2.44, and 94.4% improved versus 81.6% at 9 months, an odds ratio of 3.32. The antiviral outcome was different, with no perceived benefit: at 3 months, 71.2% on acyclovir and 75.7% not on acyclovir recovered, an odds ratio of 0.86; and at 9 months, 85.4% on acyclovir and 90.8% not on acyclovir recovered, an

odds ratio of 0.61. They concluded that early treatment with prednisolone in Bell's palsy significantly improved the chance of recovery, but for acyclovir "there is no evidence of a benefit of acyclovir given alone or an additional benefit of acyclovir in combination with prednisolone" [41]. The benefit of prednisone was present in patients with moderate facial weakness as well as severe palsy [42].

In 2008, Engstrom et al. [43] published another prospective, double-blind, randomized, placebo-controlled trial of Bell's palsy within 72 h of onset. Patients were assigned to either placebo and placebo, prednisone 60 mg for 5 days plus placebo, valacyclovir 1,000 mg three times a day for 7 days plus placebo, or prednisone and valacyclovir. Eight hundred and thirty nine patients were assigned with 829 included in the intention-to-treat analysis. The primary endpoint was the time to complete recovery. There was a significant decrease in the time to completely recover in the patients who took prednisone compared to those that did not (hazard ratio of 1.40). However, there was no difference in time to complete recovery between those patients who took valacyclovir and those that did not (hazard ratio 1.01). At 12 months, 72% of patients given prednisone recovered versus 57% for those who did not, and 58% for those given just valacyclovir. Synkinesis was seen in 14% of the prednisone-treated group but was present in 29% of the nonprednisone-treated patients.

Finally, in 2009, de Almeida et al. [44] published a meta-analysis of 18 studies, containing 2,786 patients, concerning corticosteroids and/or antiviral agents in Bell's palsy. Steroids were found to significantly reduce the risk of an unsatisfactory outcome (relative risk reduction of 0.69) with a number needed to treat to benefit one person of 11. Antiviral agents alone did not reduce the risk of poor outcome, but when combined with steroids, provided marginal benefit than steroids alone.

These studies have confirmed the benefit of corticosteroids in the acute treatment of Bell's palsy, if initiated by 72 h after onset. However, they have engendered further debate about the role of antiviral agents. A reasonable course of action based on these studies would be to treat Bell's palsy with moderate paresis with steroids alone, while reserving antiviral treatment for those patients with severe to complete palsies [10].

Other treatments have been considered but remain controversial. A Cochrane review of acupuncture in Bell's palsy found six studies with 537 patients but was unable to reach any conclusion due to poor study quality [45]. Surgical treatment of Bell's palsy has followed a changeable course, with the preferred site of decompression and timing changing over time [46, 47]. May, once an ardent advocate of surgical decompression, changed his opinion to the belief it was of no benefit [48]. A more recent multicenter, prospective trial of surgical decompression via a middle cranial fossa exposure utilized electroneurography and needle electromyography to select patients [46]. Patients seen within 3 days were placed on steroids. At 14 days, those patients with total facial paralysis and >90% decrease in motor amplitude compared to the unaffected side, and no voluntary MUPs on needle electromyography, were offered surgery. Nineteen patients who met the criteria had surgical decompression within 14 days, and 18 had good recovery. Eleven patients declined surgery and four recovered to a satisfactory degree and seven had some recovery. Another seven patients had decompression surgery after 14 days, and fared similar to those who had declined surgery. The study was not randomized or blinded in any way, and the numbers are small. But it does bring back into consideration early surgical decompression in those patients with the worst prognosis [46].

There is a lack of prospective, randomized controlled trials in Ramsay Hunt disease. The largest retrospective trial used oral prednisone and intravenous acyclovir in 80 patients, divided by onset of treatment [49]. 75% of those treated within 3 days recovered completely, down to 48% when treatment was not started until days four through seven, and only 30% had complete recovery when treatment was delayed until after 7 days [20, 49]. Oral antiviral dosages differ from what is effective for HSV, requiring 3,000 mg/day of valacyclovir or 4,000 mg/day of acyclovir for 7 days for VZV, versus 1,000 mg/day of either for 5 days for HSV [10] and as they inhibit viral replication but do not destroy viruses, treatment must be initiated within 3 days to be effective [10].

There are no prospective, randomized, controlled treatment trials for Lyme facial neuropathy. Oral antibiotics in a patient with Lyme facial neuropathy and normal CSF are appropriate [50]. Several oral and parenteral antibiotics are effective [25, 50]. The question of whether patients with Lyme facial neuropathy should have CSF examined is one of continuing debate and depends on whether oral or parenteral antibiotics are indicated if meningitis is present [50, 51]. "If, in fact, all forms of this infection-except for clinically or radiographically evident parenchymal CNS disease-are equally treatable with oral antibiotics, this would appear to be unnecessary" [25]. In endemic areas, the presence of facial palsy, with or without meningitis, with a history of tick exposure is enough to empirically initiate treatment. It is unclear whether steroids help, hinder, or have no effect either way on the recovery of Lyme facial neuropathy [50]. Treatment responses are comparable between adults and children [50].

Conclusion

The primary manifestation of facial neuropathy is unilateral facial weakness. In the emergent setting, differentiation between facial neuropathy and stroke is most important. Once facial neuropathy is established, the differential is between Bell's palsy, which accounts for most cases, and secondary causes, of which Ramsay Hunt syndrome and Lyme disease are most frequent. If seen within 72 h of onset, patients with Bell's palsy should be treated with at least a 5 day course of relatively high doses of corticosteroids (prednisone 60 mg or prednisolone 50 mg). If their facial neuropathy is severe or complete, a course of antiviral therapy directed against HSV should be considered. If vesicular lesions of the ear or mouth are present, antiviral treatment is essential. In areas endemic for Lyme disease, oral antibiotic treatment should be initiated for patients with a history of tick exposure, even if the Lyme disease ELISA is negative. Imaging and CSF examination should be reserved for those patients with facial neuropathy and high suspicion of other secondary causes, including multiple cranial neuropathies, neurologic signs or symptoms beyond the cranial nerves, fever, meningismus, and the presence of other medical diseases known to be associated with facial neuropathy.

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Acute Stroke Evaluation and Management

8

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Abstract

Stroke is the fourth leading cause of death and the leading cause of disability in the United States. Several new therapeutic strategies such as institution of recanalization therapies in the first few hours after ischemic stroke are now available to reduce death and stroke-related disability. Understanding the stroke epidemiology and pathophysiology, and knowledge of evidence-based guidelines are the cornerstones of high-quality emergent acute stroke management. Stroke is typically characterized by sudden onset of focal neurological deficits. Advanced neuroimaging (CT and MRI) can help confirm the clinical diagnosis and guide treatment. Ischemic stroke is by far

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the most common form of stroke resulting from sudden arterial occlusion in a vascular territory. Common etiologies include cardiogenic embolism, extracranial and intracranial large artery atherosclerosis, lacunar stroke, and cryptogenic stroke. In acute ischemic stroke, intravenous tPA should be given with 4.5 h after symptom onset in patients without contraindications. Endovascular therapy shows benefit in selected patients within certain time window. Most strokes after transient ischemic attack occur within 90 days, and majority within 48 h. Urgent evaluation and treatment of patient with TIA especially in high-risk patients are important. Intracerebral hemorrhage and subarachnoid hemorrhage are devastating diseases. Hypertension and smoking are common risk factors. The clinical symptoms are characterized by focal neurological deficits associated with headache and other signs of high intracranial pressure. Blood pressure management is critical in managing intracerebral hemorrhage. Recently clinical trials suggested that aggressive blood pressure reduction does not worse the outcome. In subarachnoid hemorrhage, emergent aneurysm occlusion with coiling or clipping to prevent rebleed is crucial in acute phase. Delayed cerebral vasospasm should be monitored closely. Cerebral venous thrombosis (CVT) is uncommon. Headache and seizures are the common symptoms. Anticoagulation is the primary therapy for CVT.

Keywords

Acute ischemic stroke • Intracerebral hemorrhage • Stroke • Subarachnoid hemorrhage • tPA

Introduction

Stroke is a syndrome characterized by rapidly developing clinical symptoms and/or signs of focal or global loss of cerebral function, with no apparent cause other than that of vascular origin. Stroke is the leading cause of serious and long-term disability and is the third leading cause of death in the USA. There are about 800,000 strokes each year [1]. On average, one person suffers a stroke in the United States every 40 s. Of all strokes, 87% are ischemic, 10% are intracerebral hemorrhagic, and <3% are subarachnoid hemorrhagic. Emergent management of acute stroke including differential diagnosis and application of specific therapies that are time-sensitive is of great importance in achieving good functional outcomes in stroke patients. Over the last two decades there have been exciting advances in acute stroke imaging and development of disease-modifying therapies such as thrombolysis for acute ischemic stroke (AIS). In this chapter we review the current epidemiological information, pathophysiological basis, and evidence-based clinical and imaging evaluation and treatments for acute stroke.

Epidemiology of Stroke

Acute Ischemic Stroke

The age-adjusted incidence of first ischemic stroke is 88/100,000 in whites, 149/100,000 in Hispanics, and 191/100,000 in blacks [1]. The risk of stroke doubles every decade after age 55. The prevalence of stroke is approximately 13% for individuals 60–79 years of age, but is 27% after 80 years of age [2]. The stroke incidence rate is higher for men compared with women at younger ages, but not at older ages. After it is adjusted for age, the male/female incidence rate

ratio is 1.55 [3]. The overall case fatality rate is 8.1% for ischemic stroke [4].

Transient Ischemic Attack

A transient ischemic attack (TIA) is a transient episode of neurological dysfunction caused by reduced blood flow to the brain, spinal cord, or retina without permanent death of brain tissue or acute infarct [5]. The incidence of TIA in the United States is 200,000–500,000 each year. A TIA precedes about 15% of all strokes. One-third of episodes characterized as TIA have positive diffusion-weighted magnetic resonance imaging (MRI) findings. After a TIA, the 90 days risk of stroke is 3%–17.3% and is highest within the first 30 days, with half occurring within the first 48 h after a TIA [6]. Thus, urgent evaluation and initiation of appropriate prophylactic treatment during or after a TIA is of great importance.

Intracerebral Hemorrhage

Intracerebral hemorrhage (ICH) represents 10–15% of all strokes. The mortality in ICH at 1 month is reported to be 35%–52% [7]. The case fatality rate is 45%. Half of all deaths occur within the first 2 days following an ICH. Only 20% of ICH patients live independently at 6 months [8].

Subarachnoid Hemorrhage

Subarachnoid hemorrhage (SAH) is a devastating stroke subtype that accounts for 3%–5% of all strokes. About 85% of subarachnoid hemorrhages are caused by a ruptured aneurysm. Ten percent of SAH patients have perimesencephalic hemorrhage, the cause of which is unknown [9]. In the United States, the annual incidence of SAH is about 10–20/100,000, or 30,000 cases per year [9]. The incidence of SAH increases with age, is more common in women than in men, and is more common in black Americans than in white Americans. The mortality rate for SAH is as high as 40–50% [1]. A majority of patients die in the first day after SAH.

Cerebral Venous Thrombosis

Cerebral venous thrombosis (CVT) is an uncommon type of stroke marked by clotting of blood in the cerebral veins, dural sinuses, or cortical veins. CVT is rare and accounts for fewer than 1% of all strokes [10]. Its incidence might have been underestimated in the past due to the lack of accurate diagnostic techniques. CVT is more common in young patients, and in females. The rate of CVT during pregnancy is 0.6/100,000 [1].

Etiopathogenesis

AIS and TIA

The risk factors for AIS are shown in Tables 8.1 and 8.2. AIS results from a sudden decrease in blood supply to a localized brain region, resulting in tissue death and dysfunction. Common mechanisms of ischemic stroke are cardioembolism, artery to artery embolism, small-vessel occlusion, and hypoperfusion. More than one mechanism may interact to cause brain infarction, such as hypoperfusion and embolization where a low perfusion pressure may be unable to wash out embolic material [11, 12].

Table 8.1 Modifiable risk factors and relative risk for ischemic stroke [1]

Factor	Relative risk
Cardiovascular disease	1.73 For men 1.55 For women
Hypertension	1 – 4
Cigarette smoking	1.8
Diabetes	1.8 – 6
Asymptomatic carotid stenosis	2
Dyslipidemia	1.5 – 2.5
Obesity	2.7
Atrial fibrillation	2.6 – 4.5
Physical inactivity	2.7
Postmenopausal hormone therapy	1.4

Table 8.2 Nonmodifiable stroke risk factors [3]

Age	Elderly
Race	Blacks > Hispanics > whites
Sex	Men > women
Genetics	Examples: CADASIL, sickle-cell disease, Fabry's disease

Atherosclerosis is the most common pathological feature of large vessel disease. Dissection, arteritis, and other vasculopathies, such as Moya-Moya and sickle cell-associated vasculopathy, are less common pathological conditions that affect extra- and intracranial large vessels. Atherosclerosis is a consequence of the accumulation of lipids, smooth muscle cells, fibroblasts, and calcium in response to several atherogenic stimuli. Atherosclerotic plaques can undergo pathological changes such as ulceration, thrombosis, and intraplaque hemorrhage. These processes can lead to formation of a thrombus on a plaque that can embolize, or in plaque expansion with or without superimposed thrombus, that can result in vessel occlusion. In addition to atherosclerosis, other pathological conditions could cause thrombotic occlusion of a vessel.

Embolism is the most common mechanism of stroke. Emboli can be cardiogenic, or can originate in the arteries, including the aorta, carotids, and vertebrals [13, 14]. The conditions that most commonly cause cardiac emboli are atrial fibrillation, rheumatic fever disease, post myocardiac infarction, prosthetic heart valves, and vegetation on heart valves. Paradoxical emboli occur with a patent foramen ovale. An embolus is frequently a thrombus but could be any traveling particle, including fat or debris, air, bacteria, and tumor cells.

Hypoperfusion or low flow in a vascular territory is another important stroke mechanism. Hypoperfusion can result from systemic hypotension or occur distal to a stenotic or occluded artery. Global ischemia resulting from cardiac arrest causes the greatest damage to areas between the territories of the major cerebral and cerebellar arteries known as the "boundary zone" or "watershed area" [15]. The parietal–temporal–occipital triangle at the junction of the anterior, middle, and posterior cerebral arteries is a watershed area commonly affected by global ischemia.

Intracerebral Hemorrhage

Hypertension, advancing age, smoking, African American ancestry, low LDL-c levels, and low triglyceride levels are the most important risk factors for ICH. The dominant pathological change underlying ICH is lipohyalinosis in small arteries induced by hypertension [16]. In the elderly, cerebral amyloid angiopathy is a common cause of lobar ICH. Other less common causes of ICH include vascular malformation, ruptured aneurysm, and coagulopathy, including that due to anticoagulation and antithrombotic agents. ICH is more common in men than in women, in blacks than in whites, and in Asia than in the United States and Europe [1].

Subarachnoid Hemorrhage

Hypertension, smoking, heavy alcohol abuse, and cocaine abuse are risk factors for aneurysmal subarachnoid hemorrhage [9]. There is genetic susceptibility for subarachnoid hemorrhage (SAH) in other conditions, such as polycystic kidney disease and type IV Ehlers–Danlos syndrome. Subarachnoid hemorrhage can also result from nonaneurysmal conditions, such as trauma and intracranial dissection, which predominantly occurs in the posterior circulation.

Cerebral Venous Thrombosis

The risk factors for CVT include oral contraceptive use, genetic prothrombotic state (factor V Leiden mutation, protein S, and C deficiency), infection, malignancy, and trauma. However, the postpartum period is the most common cause of CVT worldwide. About 20% of cases do not have an identified cause despite extensive evaluations [17].

Pathophysiology

Acute Ischemic Stroke

Brain tissue has a relatively high consumption of oxygen and glucose and is therefore particularly vulnerable to ischemic events. Mathematical

models have estimated that about 1.9 million neurons die every minute during an ischemic stroke [18]. The final consequence of the ischemic cascade is infarction. Depending on the time from onset of ischemic insults and on the collateral circulation, an area of potentially salvageable tissue called the ischemic penumbra surrounds the irreversible damaged tissue or infarction core. Normal cerebral blood flow (CBF) is approximately 50–60 ml/100 g tissue/min. In response to ischemia, the cerebral autoregulatory mechanisms compensate for a reduction in CBF by local vasodilatation, opening the collaterals, and increasing the extraction of oxygen and glucose from the blood. When CBF decreases below 20 ml/100 g tissue/min, electrical silence and diminished synaptic activity ensues. This correlates with the development of neurological symptoms. It is only when CBF drops below 10–12 ml/100 g tissue/min that irreversible neuronal injury occurs [19].

At the molecular and cellular level, the damage cascade initiated by ischemia is influenced by many factors, and can lead to apoptosis and necrosis. The ischemic cascade is a complex process, and is characterized by cellular energy failure resulting in excitotoxicity, oxidative stress, ATP depletion, the failure of ion transport systems, membrane depolarization, and blood–brain barrier dysfunction [20]. Excitotoxicity is triggered by depletion of cellular energy stores. Glutamate, which is normally stored inside the synaptic terminals, is normally cleared from the extracellular space by energy-dependent processes. The greatly increased concentration of glutamate in the extracellular space results in calcium influx through opening of N-methyl D-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxanole propionate (AMPA) receptors. This elevation of intracellular calcium activates enzymes involved in cell death pathways and free radical production, and ultimately leads to necrosis and apoptosis [21].

Sudden occlusion of a cerebral artery results in an infarcted core and in a surrounding ischemic penumbra. In the central core of an infarct, cerebral blood volume is decreased dramatically and cells die quickly. This region is considered irreversibly damaged. The phenomenon of penumbra was first described by Astrup and collaborators [22, 23]. In the penumbral brain tissue, the injury is thought to be reversible. Here cerebral blood flow is reduced to a critical point resulting in neuronal dysfunction, but there is sufficient energy supply to maintain cellular membrane potentials. Therefore, brain tissue in the penumbra is potentially salvageable if cerebral blood flow is restored in a timely fashion. It is estimated that salvageable tissue is initially present in up to 80% of AIS patients, but decreases over the first 6–12 h after symptom onset [22, 24]. Surrounding the infarct core and penumbra is a region of benign oligemia where the CBF is lower than normal but not low enough to cause irreversible damage over time. This region of benign oligemia does not progress to infarction.

Intracerebral Hemorrhage

About 50% of ICHs are deep in location, 35% are lobar, 10% are cerebellar, and 6% are located in the brainstem [25]. The factors related to mortality and morbidity include the baseline ICH volume, intraventricular extension with hydrocephalus, growth of the volume of ICH in the first few hours after hemorrhage, baseline clinical state, and an infratentorial location [26]. Substantial growth in the volume of an ICH occurs soon after its onset. About 72% of ICHs have some hematoma expansion over the first 24 h. In one-third of these cases, the hematoma expansion is significant. Most of this growth occurs within the first 4 h after onset and is true for all locations of ICH. Although still debated, evidence is growing that there is no perihematoma ischemic penumbra. The low-density region surrounding the hematoma on cerebral imaging appears to be caused by diffusion of fluid and proteins [27].

Subarachnoid Hemorrhage

Addition of subarachnoid blood products into the intracranial compartment causes a significant increase in intracranial pressure (ICP) and results in a chemical meningeal irritation. The high

ICP causes reduction in cerebral blood flow and malfunction of cerebral autoregulation, and eventually results in decreased cerebral perfusion and cerebral ischemia [28]. The rate of recurrent aneurysmal subarachnoid hemorrhage is maximal (4%) on the first day after an SAH, and then decreases to 1–2% per day over the next 4 days. In the first 2 weeks after aneurysmal SAH, the risk of rebleeding from an unsecured aneurysm is as high as 20% [28]. The consequence of rebleeding is severe with a fatality rate of 70% [29]. Delayed admission and treatment, higher initial blood pressure, and worse initial neurological status are associated with a high recurrent hemorrhage rate.

Delayed cerebral ischemia is associated with the development of intracranial arterial vasospasm in response to exposure to subarachnoid blood products. Mechanical reductions in blood flow, endothelial dysfunction, inflammation, and genetic susceptibility have all been implicated in the delayed cerebral ischemia that accompanies SAH. With early securing of aneurysms, delayed cerebral ischemia is now the main cause of disability in aneurysmal SAH.

Clinical Presentation

Acute Ischemic Stroke

The clinical syndrome of ischemic stroke is typically characterized by the sudden onset of focal neurological deficits. Less commonly, stroke can manifest itself as a sudden alteration in consciousness without prominent focal neurologic deficits, particularly in basilar occlusion. The symptoms of stroke reflect the areas of the brain that are affected by the focal ischemia. Table 8.3 summarizes the main clinical findings according to the main arterial branch involved.

Clinical localization of brain injury in AIS is an important step in evaluation of the patient, but should not delay the administration of intravenous tPA or triage to endovascular recanalization therapy (ERT) for AIS.

Large vessel strokes involve the middle cerebral artery, the anterior cerebral artery, and the basilar artery and its major branches. Small-vessel strokes (lacunar infarction) are generally attributed to lipohyalinosis and/or thrombotic occlusion of diseased arteries. Which vessels are occluded can be determined by examining the location and degree of weakness in the face, arms, and legs. Lesions of the MCA often involve weakness of the face and arm, sparing the leg. In contrast, in an ACA infarct, leg weakness is seen, and the face and arm are spared. In small-vessel syndromes, patients will present with weakness in the face, arm, and leg equally. Motor and sensory involvement also helps localize the affected vessels. Large vessel infarctions are commonly associated with both weakness and sensory loss. Small vessel strokes, in contrast, usually lead to either weakness or sensory loss. Aphasia, neglect, visual field defect, and gaze deviation contralateral to the side of brain ischemia are the four classic signs of

Table 8.3 Clinical presentation of acute ischemic stroke

Location	Signs and symptoms
ACA distribution	Contralateral leg > face and arm weakness and sensory loss, apathy, incontinence, abulia, and transcortical aphasia depending on which hemisphere is involved
MCA distribution	Face, arm > leg weakness and sensory loss, aphasia (dominant hemisphere) or neglect (nondominant hemisphere)
PCA distribution	Homonymous hemianopia and alexia without agraphia if the corpus callosum of the dominant hemisphere is involved, rarely hemiparesis if the cerebral peduncle is involved
Posterior circulation	Vertigo, vision changes (blurred vision or diplopia), ataxia, quadriparesis, and mental status changes. Features strongly suggestive of brainstem involvement include crossed signs involving ipsilateral cranial nerves and contralateral body
Ophthalmic artery	Monocular visual loss (transient amaurosis fugax or permanent central or branch retinal artery occlusion), often described as blurring, graying, or curtaining of vision
Anterior choroidal artery	Affects the basal ganglia and internal capsule, with contralateral hemiplegia, hemisensory loss, and hourglass-shaped homonymous visual field defects. Anterior choroidal infarcts may be difficult to differentiate from lacunar strokes due to occlusion of small penetrators

cortical injury seen in large vessel occlusion. However, these signs are not exclusive to cortical injury from large vessel occlusion and aphasia can be seen in subcortical thalamic infarcts and gaze deviation can be present in brainstem infarction.

Small-artery occlusion can be recognized clinically when they result in lacunar syndromes. There have been over 20 lacunar syndromes described. Four of them have distinct clinical syndromes that accurately predict their localization. Pure motor lacunar infarcts are usually localized in the posterior limb of the internal capsule and basis pontis, and in the corona radiata. Pure sensory strokes are usually found in the thalamus or thalamocortical projections. Ataxia hemiparesis results from lacunar infarcts in the pons or corona radiata due to the involvement of pontocerebellar fibers. A variant of ataxia hemiparesis is dysarthria clumsy hand syndrome. Brainstem infarction usually is seen in patients who present with "crossed signs": cranial nerve abnormalities on one side and weakness on the other side.

Carotid dissection often results in an incomplete Horner's syndrome due to compression of the nerve fibers from third-order neurons of the sympathetic pathway ascending up the carotid plexus. Incomplete Horner's signs include ptosis and miosis without anhidrosis.

Intracerebral Hemorrhage

The clinical signs of intracerebral hemorrhage are difficult to distinguish reliably from ischemic stroke. The classic ICH presentation is a sudden onset of a focal neurological deficit with an associated headache, decreased level of consciousness, and elevated blood pressure. The most common localization of hypertensive-related intracerebral hemorrhage is the putamen. Compared with AIS and SAH, more patients with ICH present with gradual progression of symptoms, which is frequently due to ongoing bleeding and an enlarging hematoma. Compared with AIS, decreased levels of consciousness and headaches are more common with ICH. Seizures are not common with deep hematomas.

Subarachnoid Hemorrhage

The typical clinical presentation of SAH is a complaint about "the worst headache in my life." The description of such thunderclap headache is reported by about 60% of patients. Some patient will have milder headaches in the days and weeks prior to SAH, felt to be due to small leaking (sentinel bleed) or expansion of the aneurysmal sac [30]. Other associated symptoms include nausea, vomiting, altered mental status, and nuchal rigidity. The level of consciousness varies from drowsiness to coma. About 20% of patients will have seizures.

Cerebral Venous Thrombosis

Headache is the most common presenting symptom of CVT (75%). Seizures are reported in 50% of patients with CVT. This percentage of seizures is even higher in peripartum women [31]. Other neurological symptoms, like nausea, visual disturbances, papilledema, and alterations in mental status are associated with increased intracranial pressure. Headache, seizures, and papilledema form the classic triad of CVT. Coma and stupor are associated with poor prognosis and high mortality.

Emergency Diagnostic Approach and Treatment

Neurological symptoms that begin abruptly suggest a vascular etiology. After the patient's airway, breathing, and circulation (ABC) have been stabilized, a health-care professional may proceed with a systematic diagnostic approach to confirm a vascular cause of symptoms, exclude stroke mimics, and select patients eligible for acute therapies. This approach includes accurately establishing when symptoms started, performing a focused neurological assessment, and interpreting neuroimaging studies. If a precise time of symptom onset is impossible to determine, efforts should be made to identify when the patient was last neurologically normal.

Acute Ischemic Stroke

Diagnosis

The FDA approval of intravenous thrombolytics for AIS led to a major paradigm shift in AIS therapy [32]. More recently, the American Heart Association has endorsed an extension of the IV tPA time window to 4.5 h [33]. An urgent initial evaluation is geared to determine if a patient is eligible for acute revascularization interventions. Contraindications to thrombolysis include [1] a time of ischemic stroke onset beyond the 4.5 h window, determined by interviewing the patient or witnesses, [2] a prior surgery or a record of bleeding, obtained through a focused history, [3] coagulopathy identified in the history or by laboratory testing, and [4] exclusion of an intracerebral hemorrhage or a large area of cytotoxic edema through use of cerebral imaging.

The ability to treat AIS patients with IV thrombolysis or endovascular therapies depends on accurately establishing when symptoms started. The patient, relatives, witnesses, and even paramedics are useful sources of this information. Administration of thrombolytics after the approved time is ineffective and may result in cerebral hemorrhage. Patients who wake up with neurological deficits must be assumed to have had onset of symptoms at bedtime or the last time they were observed to be normal.

The neurological examination should focus on identifying signs of lateralized hemispheric or brainstem dysfunction or focal deficits that are consistent with focal cerebral ischemia. A quick determination of the patient's NIH stroke scale (NIHSS) should be done. The NIHSS is a well-validated instrument that quantifies the neurologic exam and is used to measure stroke severity [29, 34]. Other conditions presenting with focal neurological deficits that mimic AIS should be differentiated. These include Todd's paralysis, complicated migraine, hypertensive encephalopathy, reactivation of prior deficits, conversion reaction, and peripheral vestibulopathy. Among patients who received IV tPA, 3.5%–14% had stroke mimics [35]. The stroke mimics most commonly seen were seizures, complicated migraines, and conversion disorders. Patients who present with stroke mimics are usually younger and have fewer risk factors for AIS. In one recent case series, when IV tPA was inadvertently given to stroke mimics, no instances of symptomatic ICH were found [35].

The laboratory tests for potential AIS patients should include a complete blood count, blood electrolytes and glucose levels, prothrombin time, activated partial thromboplastin time, the international normalized ratio, and renal function parameters. The rationale to order these tests is to determine if contraindications to thrombolysis exist. Cardiac enzymes and a 12-lead EKG are recommended for all stroke patients.

A noncontrast head CT scan is the study of choice at most centers for emergent AIS evaluation. A CT scan helps detect intracranial blood and early ischemic changes, including loss of differentiation in the gray–white matter interface, particularly in the region of the insular cortex or the lentiform nucleus, sulcal effacement, and a hyperdense artery sign. However, early ischemic changes by themselves are not a contraindication for IV tPA. Advanced brain imaging to assess vessel patency and to estimate the amount of penumbral tissue [with CT angiogram and CT perfusion or MRI (diffusion and perfusion) and magnetic resonance angiography (MRA)] are potentially useful in selecting patients eligible for endovascular therapy, namely, those with large vessel occlusion and with salvageable brain tissue [3, 36–39]. However, use of these modalities is an evolving area in the emergent evaluation of AIS. Advanced imaging is not indicated in selecting patients for IV tPA and adds harmful delays in treating the patient with standard of care as early as possible. Beyond the 3 (or 4.5) h window or when endovascular therapy is the only option, advanced imaging may play a role in selecting AIS patients in whom the potential benefits of acute ERT outweigh the risks. While a 20% or more "mismatch" between the area of irreversibly injured brain tissue and the area of tissue at risk (penumbra) is a frequently used criterion for selecting patients for ERT, better selection criteria will most likely emerge from ongoing studies such as MR RESCUE.

Table 8.4 Acute stroke treatment guidelines

Class 1, level of evidence A: benefit > risk, should be performed, based on multiple randomized clinical trials • IV rtPA < 3 h
Class 1, level of evidence B: benefit > risk, should be performed, based on a single randomized clinical trial or multiple nonrandomized trials • IV rtPA 3–4.5 h • Intra-arterial (IA) thrombolysis for MCA occlusion < 6 h
Class 2a, level of evidence B: benefit > risk, reasonable to perform, based on a single randomized clinical trial or multiple nonrandomized trials • Mechanical thrombectomy with devices clot retriever and thromboaspiration devices FDA approved <8 h

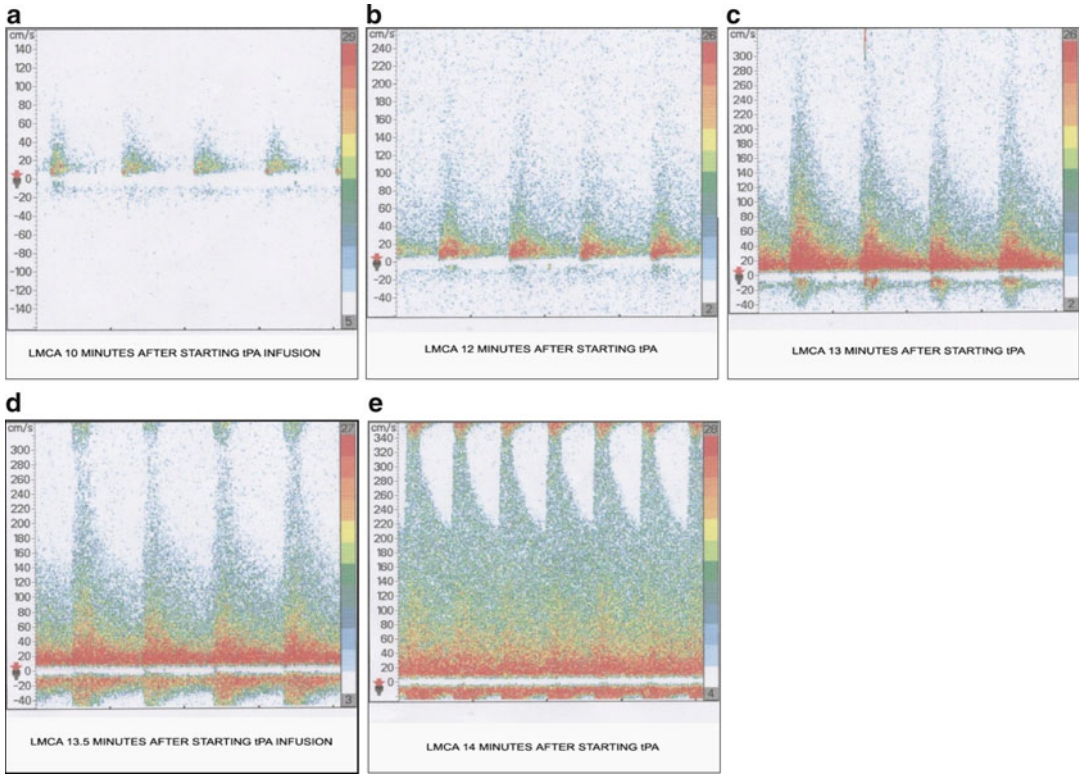

Fig. 8.1 A 71-year-old male with acute onset left MCA (LMCA) syndrome at 2 h from symptoms onset. Given IV tPA at 2.5 h. Continuous monitoring of intracranial vessel status by transcranial Doppler (TCD) during IV tPA infusion showing rapidly improving flow indicating recanalization of the LMCA. **a**, TCD showed L MCA occlusion. **c**–**e**, TCD showed gradual recanalization of L MCA after IV tPA

Acute Treatment

The objective of AIS treatment is to salvage penumbral tissue. Revascularization is the most effective intervention for restoring blood flow to ischemic tissue and is highly recommended by the American Heart Association Guidelines for treatment of Acute Stroke, as noted in Table 8.4 [40].

Intravenous Chemical Thrombolysis

Thrombolytic therapy in carefully selected AIS patients is the cornerstone of AIS treatment. Once an AIS is suspected, eligible patients should be treated with IV rtPA as soon as possible (Fig. 8.1). The Food and Drug Administration has approved IV rtPA for AIS within 3 h of symptom onset based mainly on the results of the NINDS tPA

Table 8.5 IV rtPA indications and contraindications in acute ischemic stroke

Inclusion criteria
1. Diagnosis of ischemic stroke causing measurable neurological deficit
2. Onset of symptoms < 3 h before beginning treatment
Exclusion criteria
1. Prior stroke or head injury within the last 3 months
2. Major surgery within the last 14 days
3. Gastrointestinal or urinary tract hemorrhage within the past 21 days
4. Arterial puncture at a noncompressible site within the last 7 days
5. Systolic blood pressure >185 or diastolic blood pressure >110 mm Hg
6. Received heparin within the past 48 h and currently has an elevated partial thromboplastin time
7. INR > 1.7
8. Platelets <100,000
9. Glucose < 50 or >400 mg/dl
10. Rapidly improving or minor symptoms
11. CT scan shows a hypodensity greater than one-third of the MCA distribution

Table 8.6 Timeline for completing evaluations and starting treatment of acute ischemic stroke

Time interval	Time target (min)
Door to doctor	10
Access to neurological expertise	15
Door to CT scan completion	25
Door to CT scan interpretation	45
Door to needle (treatment with IV tPA)	60

study [32]. This US-based study compared IV rtPA vs. placebo in 624 patients. IV rtPA-treated patients were 30% more likely to have a favorable outcome with no or minimal disability after 3 months. This remains a Class IA AHA recommendation [31]. IV rtPA treatment benefits patients suffering from any ischemic stroke subtype including cardioembolic, atherothrombolic, and lacunar infarcts. For every 100 patients treated with IV tPA within 3 h, 32 will benefit and 3 will be harmed. Although hemorrhagic transformation is common after ischemic stroke, particularly in embolic strokes, the great majority of patients are asymptomatic. Symptomatic deterioration due to hemorrhagic transformation of an ischemic stroke is related to a mass effect from added blood products, and is increased with IV rtPA compared to placebo. In the NINDS study, the hemorrhage rate with IV tPA within 3 h is 6.4%. The inclusion and exclusion criteria for IV rtPA are presented in Table 8.5.

Recent AHA guidelines recommend extension of the IV rtPA treatment window to 4.5 h, based on results of the European Cooperative Acute Stroke Study (ECASS) III trial [33]. In this extended time window, for every 100 patients treated, 16 will benefit and 3 will be harmed. An independent functional outcome (modified Rankin Scale 0–1) was more likely with IV rtPA (52.4% vs. 45.7%). The symptomatic intracranial hemorrhage rate was 7.9%, similar to that in a ≤3 h window. At the time of this writing, the FDA has not yet approved this time window for IV rtPA, and the extended time window has not yet been consistently implemented in the USA [32, 33]. The ECASS III trial used additional exclusionary criteria: age >80, NIHSS >25, and the combination of prior stroke and diabetes mellitus. Future recommendations may modify these additional exclusionary criteria. Beyond 4.5 h, no current data support a benefit of IV rtPA treatment [33, 41].

Patients with AIS benefit from IV tPA when treated within 4.5 h of onset. Treatment with IV tPA is usually initiated in the emergency department. tPA is administered at a dose of 0.9 mg/kg, up to a maximum dose of 90 mg. Ten percent of the total dose is given as a bolus, and the remainder is given over 1 h as an infusion. Antiplatelet drugs, anticoagulants, and invasive procedures are avoided in the next 24 h. The blood pressure should be monitored closely to ensure that the systolic blood pressure is kept below 180 Hg or that the diastolic blood pressure stays below 105 mg Hg.

As every minute is critical, it is crucial to meet the recommended time guidelines for starting IV thrombolytic therapy (Table 8.6). The initial physical and neurological exam should be completed within 10 min of the patient's arrival. Within 25 min, the patient should have completed a noncontrast CT scan of the brain. Under any circumstance, the patient should have received IV tPA treatment in less than 60 min from arrival to an emergency room since the benefit of IV tPA treatment decreases as time from stroke onset to treatment increases.

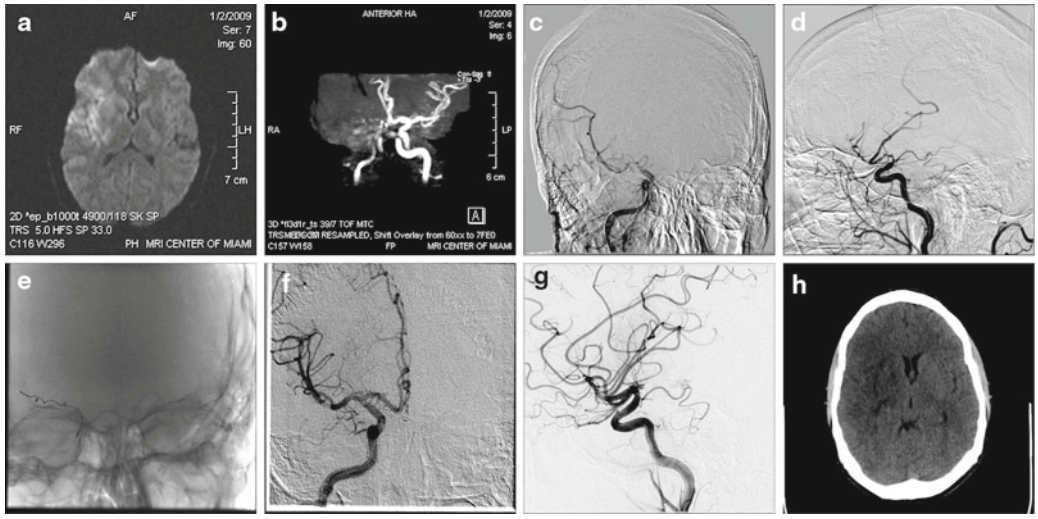

Fig. 8.2 A 28-year-old male with acute left sided weakness while jogging. NIHSS was 16 when 5.5 h from symptom onset. He received IV tPA (0.9 mg/kg) and mechanic thrombectomy. He was discharged with NIHSS of 3. (**a**) DWI showed restrictive diffusion in R MCA distribution. (**b**) MRA showed decreased flow in R ICA and MCA. (**c**, **d**), Angiogram showed T occlusion of R ICA. (**e**) showed MERCI clot retriever in R MCA/ICA. (**f**, **g**), Postthrombus retrieval angiogram showed recanalization of R ICA/MCA. (**h**), CT on day 10 showed final infarct size

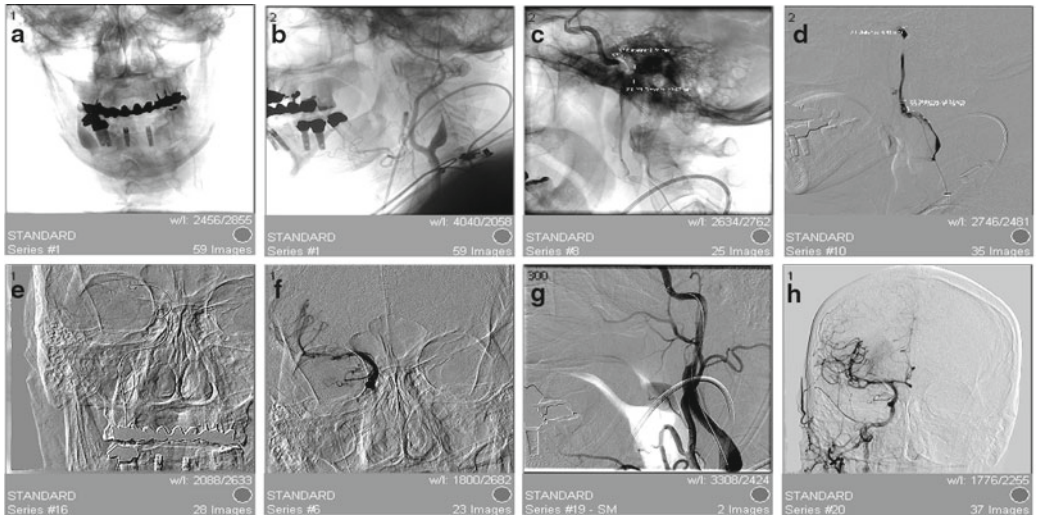

Fig. 8.3 A 60-year-old male with acute onset R vision loss and L hemiplegia with NIHSS of 13. There was slight improvement after IV tPA started at 20 min postonset. He received IA tPA and emergency carotid stenting. He was discharged on day 2 with NIHSS of 0. (**a**–**d**), Angiogram showed dissection of entire cervical ICA segment, measured 8 cm in length. (**e**, **f**), Angiogram post-IA tPA 5 mg into occluded mid-MCA (M1). (**f**, **h**), Reconstruction of R ICA with 3 telescoping intracranial + 1 carotid stents with complete recanalization

Endovascular Approaches to Acute Ischemic Stroke

Endovascular recanlization therapy (ERT) is evolving as a promising treatment for AIS. The endovascular approach has various advantages over intravenous therapy. One advantage is that it has a treatment time window that extends to 8 h after symptom onset. Another advantage is that it is more effective in the presence of a large clot burden occluding more proximal vessels, such as the internal carotid, basilar, and proximal middle cerebral artery (Figs. 8.2. and 8.3). The endovascular

approach also allows visualization of the vascular occlusion. Visualization helps avoid the unnecessary use of thrombolytics in those patients who have spontaneous recanalization and allows the use of mechanical lysis techniques that may accelerate recanalization. In addition, for patients who are ineligible for systemic thrombolysis, such as recent surgical patients or patients with a coagulopathic condition, mechanical lysis alone or with very small intraclot application of thrombolytics is safer. However, the endovascular approach requires specialized centers and operators, which limits its global application, and is accompanied by delays in therapy. Therefore, it is reserved for those patients who begin receiving medical attention between 4.5 and 8 h poststroke, or even later for select cases, such as basilar occlusion [40].

The data supporting the use of endovascular approaches comes from various single-center studies and from one multicenter study. The PROACT II study, a phase 3 trial of intra-arterial pharmacologic fibrinolysis for patients with M1 or M2 middle cerebral artery occlusion up to 6 h from symptom onset, demonstrated improved recanalization (66% of those treated vs. 18% of controls) and improved functional outcomes (3-month modified Rankin Scale ≤2 in 40% of those treated vs. the same score in 25% of controls) [42].

Intra-arterial thrombolysis is recommended as a treatment option for major strokes caused by MCA occlusion as long as that treatment occurs within 6 h poststroke. This is a Class I recommendation by the AHA with level B evidence. Treatment requires qualified interventionists at experienced stroke centers with the necessary facilities [40]. A number of other multicenter clinical trials are now under way to confirm the utility of penumbra imaging to triage patients for endovascular therapy, and to evaluate if combination IV and endovascular treatment are superior to IV rtPA treatment alone.

Early Supportive Treatment of Acute Ischemic Stroke

Early supportive treatment of stroke includes avoidance of systemic oxygen desaturation, hyperthermia, hyperglycemia, and dehydration (Table 8.7). Blood pressure should be closely monitored and hypotension should be avoided. In ischemic stroke, cerebral autoregulation is lost. Therefore, changes in blood pressure can result in hyper- or hypoperfusion of the ischemic tissue, and abrupt drops in blood pressure may cause failure of collateral circulation and extend the infarct core. The current recommendation is to withhold antihypertensive medications unless the systolic blood pressure is greater than 220 or the mean arterial pressure is greater than 130. If thrombolytics are employed, then the SBP should be kept under 180 mm Hg, and the diastolic BP under 105. If an elevated BP needs reduction, short-acting agents such as nicardipine or labetolol are preferred. Vasodilators, particularly nifedipine, should be avoided as they can produce a precipitous drop in BP, resulting in a reduction of cerebral blood flow to the ischemic penumbra. In the presence of overt cardiac failure, coronary ischemia, or aortic dissection, BP needs to be reduced more energetically. Antithrombotic therapy may prevent clot extension or recurrent embolization. Antiplatelet drugs (aspirin, aspirin + dipyridamole, and clopidogrel) are of benefit when started within 48 h of a stroke. Administration of full-dose unfractionated or low molecular weight heparin is not recommended in the acute setting of an ischemic stroke as the risk of hemorrhage is greater than the potential benefit of preventing recurrent ischemic events [31, 40]. In those patients treated with thrombolytics, antithrombotics, including antiplatelet agents and subcutaneous heparin for DVT prophylaxis, should be withheld for 24 h, after which they can

Table 8.7 General management of acute ischemic stroke

Blood glucose	Avoid hypo- or hyperglycemia
Blood pressure	Avoid hypotension or excessive hypertension
Cardiac monitor	Continuous monitoring
Intravenous fluids	Avoid D5W and excessive administration of IV fluid. IV isotonic saline at 75 ml/h
Oxygen	Avoid hypoxemia
Temperature	Avoid hyperthermia
Oral intake	Nothing by mouth (NPO) until speech evaluation

Table 8.8 ABCD2 scores

ABCD2	Points	
Age	1	If > 60
Blood pressure	1	If > 140/90
Clinical symptoms	2	Points for unilateral weakness
	1	Point for only speech disturbance
Diabetes	1	If positive in history
Duration	1	Point for less than 1 h
	2	Points for more than 1 h

be restarted if cerebral imaging does not show hemorrhagic transformation of the infracted tissue. Mechanical DVT prophylaxis can be employed during this period.

Transient Ischemic Attack

The typical TIA lasts less than 1 or 2 h but can persist up to 24 h. Patients with TIAs should be evaluated based on risk stratification. The California score, ABCD score, and the newer ABCD2 score have been used in the clinic settings for risk stratification (Table 8.8). The risk of stroke in 2 days increases as the ABCD2 score increases. The risk is 0% for scores of 0–1 but 8.1% for scores of 6–7 [5]. Patients with high ABCD2 scores should be hospitalized for close observation and have an inpatient stroke workup.

Intracerebral Hemorrhage

A CT scan of the brain is the most commonly used imaging technique for evaluating a suspected ICH. AHA guidelines recommend CT scans and MRI as first-choice imaging options for suspected ICH [43]. Several prospective studies have demonstrated that an MRI is equivalent in effectiveness to CT scans for identification of an acute ICH, and is better for detection of a remote hemorrhage (hemosiderin) [44]. CT scans and MRI angiography are useful for identifying secondary causes of ICH, such as arteriovenous malformation (AVM), and for detecting extravasation indicative of ongoing bleeding but are not routinely recommended.

In the first few hours following an ICH, the most critical step is to stop or slow the bleeding. After the bleeding has been stabilized, the removal of blood may be considered in a small subgroup of patients with worsening exam under observation or cortical hemorrhages. Finally, it is important to take care of complications, such as increased intracranial pressure, mass effect, and seizures.

Blood pressure management is being investigated as a way to stop or slow bleeding during an acute ICH, but clinical trials have so far produced no clear results regarding what the parameters of blood pressure management should be. Current AHA guidelines for blood pressure management of acute spontaneous ICH include the following: If SBP is >200 mm Hg or MAP >150 mm Hg, aggressive blood pressure reduction should be considered with continuous intravenous infusion of short-acting antihypertensive agent, and blood pressure should be monitored every 5 min. If SBP is >180 mm Hg or MAP is >130 mm Hg and there is evidence or suspicion of an elevated ICP, reducing the blood pressure to keep cerebral perfusion pressure >60–80 mm Hg should be considered along with ICP monitoring. If SBP is >180 mm Hg or MAP >130 mm Hg and there is no evidence or suspicion of elevated ICP, a modest blood pressure reduction to keep blood pressure <160/90 or MAP < 110 should be considered along with a clinical exam every 15 min [43].

Recently, the Interact and ATACH Trials indicated that an early intensive blood pressure reducing treatment is clinically feasible. It is well tolerated and reduces hematoma growth. But there is no difference in the 3-month outcome [45, 46]. The results did indicate that aggressive reduction of blood pressure does not worsen the clinic outcome. This was consistent with the concept that no ischemic area surrounds a hematoma. The results of these trials suggest that aggressive measures to lower blood pressure during an acute ICH might be safe. More data from this study will be forthcoming as it has entered phase III at the time of this review.

No other medical therapies, such as the use of steroids or factor VIIa, have unequivocally improved the outcome of ICH. A phase II trial

provided evidence that treatment of acute ICH with factor VIIa within 4 h reduced the growth of the hematoma and improved the clinical outcome at 3 months [47]. However, the phase III FAST trial did not demonstrate a clear clinical efficacy even though it replicated the phase II finding of decreased hematoma growth [48].

In general, surgical removal of blood from an ICH has not been an effective treatment. However, in some cases, such as small volume ICHs, minimal intraventricular hemorrhage (IVH), or treatment times within 2 h for young patients, surgical removal of blood may be potentially beneficial [49].

For patients with warfarin-related ICH, prothrombin complex concentrate, rFVIIa, or fresh frozen plasma are recommended treatments.

Subarachnoid Hemorrhage

A noncontrast CT scan is very sensitive for detecting subarachnoid blood. The sensitivity is >95% in the first 12 h, and declines to 90% after 24 h. If an SAH is suspected but the CT scan is negative, a lumbar puncture is required to detect the xanthochromia in the CSF that may be present 6–12 h after a hemorrhage. CT angiography (CTA) is a less-invasive alternative to cerebral angiography for the detection of cerebral aneurysm causing the SAH. The sensitivity of CTA depends on the location and size of the aneurysm. In general, the sensitivity and specificity of CTA are reported to be 77–100% and 79–100%, respectively. MRI is rarely used in the diagnosis of SAH, but GRE sequence is sensitive for any form of intracranial hemorrhage. FLAIR sequences are useful in diagnosing SAH in the subacute time period when the sensitivities of CT and lumbar puncture for detecting SAH are low.

The Fisher grading score is used to estimate the blood volume and the risk of vasospasm. It is now recognized that not only cisternal but also intraventricular blood increases the risk of vasospasm [50]. The Hunt and Hess scale is used to estimate the severity and prognosis of SAH.

Initial care of SAH should focus on securing the aneurysm and preventing rebleeding. Two techniques used to prevent rebleeding are coil embolization and clip ligation of the aneurysm. Acute hydrocephalus should be treated with ventriculostomy. The Hunt and Hess clinical grading score should not be assigned until a ventriculostomy has been performed on patients with hydrocephalus [51]. Blood pressure should be monitored closely. Severe hypertension should be treated, but sudden drops in blood pressure that could result in hypoperfusion of brain tissue should be avoided. While no guidance exists regarding what blood pressure levels are appropriate, some evidence suggests that the systolic blood pressure should be kept less than 160 mm Hg.

Anticonvulsants are not recommended for prophylactic use in conjunction with SAH and should be reserved for patients with documented clinical or electrographic seizures. Supporting this recommendation is the finding that prophylactic use of phenytoin was associated with a poor outcome of SAH [52].

Ruptured aneurysms should be treated as soon as possible with endovascular coil embolization or clip ligation to prevent rebleeding. This should always be attempted before the fourth day after bleeding when the risk of vasospasm rises. Surgical clipping or endovascular coiling are both effective ways to secure the ruptured aneurysm. The ISAT trial showed that endovascular coiling was associated with a lower risk of death or dependency at 1 year compared with surgical clipping for aneurysms [53]. In most large centers in the USA, these two techniques are used to complement each other. SAHs in patients with posterior circulation aneurysms, a poor Hunt Hess grade (=or>3), or age>60 are commonly treated with an endovascular approach. Patients less than 60 years of age, with wide-neck patients or with Hunt Hess Grades=or <3, are often treated with clipping if there are experienced neurovascular surgeons at the center.

Over 60% of patients with aneurysmal subarachnoid hemorrhage (aSAH) develop cerebral vasospasm (cVSP), and half of these patients are symptomatic. A cVSP can cause delayed cerebral ischemia and significant morbidity and mortality.

The risk of cVSP increases between the third and seventh days after aSAH. Hemodynamic augmentation ("triple H" therapy) and endovascular therapy, including transluminal balloon angioplasty and intra-arterial infusion of vasodilators, have been the main treatments for cVSP [54]. The cerebral vasospasm is increasingly regarded as a disorder of endothelial function. There are preliminary clinical studies reported for statins, magnesium sulfate, and clazosentan (an endothelin antagonist) as treatments for cVSP, but the results are inconclusive. Multicenter studies are needed to clarify what treatments may be effective against cVSP.

Cerebral Venous Thrombosis

CVT is often suspected on contrast head CT scans when edema, hemorrhagic infarction, a cord sign (hyperdense thrombosed cortical vein), and a dense triangle sign (thrombus in the posterior aspect of the superior sagittal sinus) are found. On CT scans with contrast, the empty delta sign (nonfilling of the superior and transverse sinuses) is a classic finding. MRI and MRV are the best imaging techniques for evaluating CVT [55, 56]. In the subacute to acute phases, hyperintensities on DWI MRI at the site of the venous occlusion can be identified in 14%–41% of cases with CVT. DWI MRI might then be of value in predicting the risk of persistent venous occlusion at 3 months [57].

Anticoagulation is the primary therapy for CVT, but anticoagulation must be used with caution in patients with hemorrhagic infarction. Intravenous heparin is recommended by most neurologists.

Conclusions

Emergency management of acute stroke has undergone a major change in the last two decades. It is important for physicians and health-care workers to apply these new evidence-based approaches to management of patients with this often devastating condition. Especially in the case of AIS, disability limiting therapies are now available but are effective only in the first few hours after symptoms onset. With a system-based approach, hospitals treating acute stroke patients can improve the number of patients receiving effective therapies and improve outcomes.

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Intracerebral Hemorrhage

9

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and J. Claude Hemphill III

Abstract

Intracerebral hemorrhage (ICH) accounts for 10–15% of all strokes but results in a disproportionately high morbidity and mortality. While chronic hypertension accounts for the majority of ICH, other common causes include cerebral amyloid angiopathy, sympathomimetic drugs of abuse, and underlying cerebral vascular anomalies. Validated baseline predictors of clinical outcome after ICH include the initial Glasgow Coma Scale score, hematoma volume, presence and amount of intraventricular hemorrhage, infratentorial ICH location, and advanced age. Although no treatment of proven benefit currently exists for ICH, several recent large clinical trials have demonstrated the feasibility of investigation of surgical and medical treatments for ICH. Clinical research into ICH mechanisms of injury has demonstrated that hematoma expansion is common, even in patients without coagulopathy. Basic research has suggested that perihematomal injury is more likely related to toxicity of blood and iron in the brain ("neurohemoinflammation") rather than primary ischemic injury. Current guidelines for ICH treatment emphasize blood pressure management, urgent and rapid correction of coagulopathy, and surgery for

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cerebellar ICH. Ongoing clinical trials are investigating surgical evacuation of lobar hemorrhage, minimally invasive surgical hematoma evacuation, and aggressive blood pressure lowering.

Keywords
Hematoma expansion • Hypertension • Intracerebral hemorrhage • Neurocritical care

Intracerebral hemorrhage (ICH) is a common neurologic emergency. It is defined as bleeding into the brain parenchyma that is distinct from subarachnoid hemorrhage (SAH) and isolated intraventricular hemorrhage (IVH). It is expected that the incidence of ICH will increase as the overall population ages [1]; thus, intimate knowledge of this entity is important for a wide variety of medical practitioners from the emergency room to the intensive care unit (ICU). Neurologists play an essential role in the care of these patients and are often the only practitioner with a longitudinal understanding of the spectrum of ICH care, including the emergency room, ICU, and long-term outcome. In addition to participating in day-to-day medical management, neurologists are often relied upon to make critical decisions regarding the utility of emergency interventions, determination of prognosis, and more recently in the design and implementation of basic research and clinical trials of novel therapeutics for the acute treatment of ICH.

Epidemiology

ICH accounts for 10–15% of the approximately 700,000 annual strokes in the USA [1]. The incidence of ICH in the USA is approximately 12–15 cases per 100,000 [2]. Primary ICH is due to rupture of small arterioles. In most cases it is due to the effects of long-standing hypertension on these small vessels, accounting for approximately 60–70% of all ICH [3]. Cerebral amyloid angiopathy (CAA) is an increasingly recognized cause of primary ICH, particularly in elderly patients. Recurrent hemorrhage risk from amyloid deposition is tripled with the presence of the ε(epsilon)2 and ε(epsilon)4 alleles of the apolipoprotein E gene [4]. Secondary ICH occurs in the context of an underlying pathology that predisposes the patient to hemorrhage (e.g., vascular malformation or tumor). Other important etiologies of both primary and secondary ICH include coagulopathy, sympathomimetic drugs of abuse, vasculitides, and moyamoya (Table 9.1). The etiology of ICH is usually ascribed from consideration of the combination of the clinical presentation, patient risk factors, and imaging characteristics of the hemorrhage. Typical locations for hypertensive ICH include the basal ganglia, thalamus, cerebellum, pontine tegmentum, and deep lobar white matter (Fig. 9.1). Hemorrhages due to CAA are usually located in the peripheral lobar white matter near the gray and white matter interface.

Table 9.1 Etiology of nontraumatic intracerebral hemorrhage

Primary ICH	Secondary ICH
Hypertension	Vascular malformations
Cerebral amyloid angiopathy	Arteriovenous malformation
Sympathomimetic drugs of abuse Cocaine Methamphetamine	Cavernous malformation Saccular aneurysm Mycotic aneurysm
Coagulopathy	Dural arteriovenous fistula
	Moyamoya Ischemic stroke (hemorrhagic conversion) Cerebral venous sinus thrombosis (hemorrhagic conversion) Tumor (primary or metastatic) Cerebral vasculitis

Recent meta-analysis and study of pooled prospective data continue to refine our understanding of the risk factors for ICH. Hypertension, age, ethnicity, high alcohol intake, and lower LDL-C have all been variably reported to contribute to

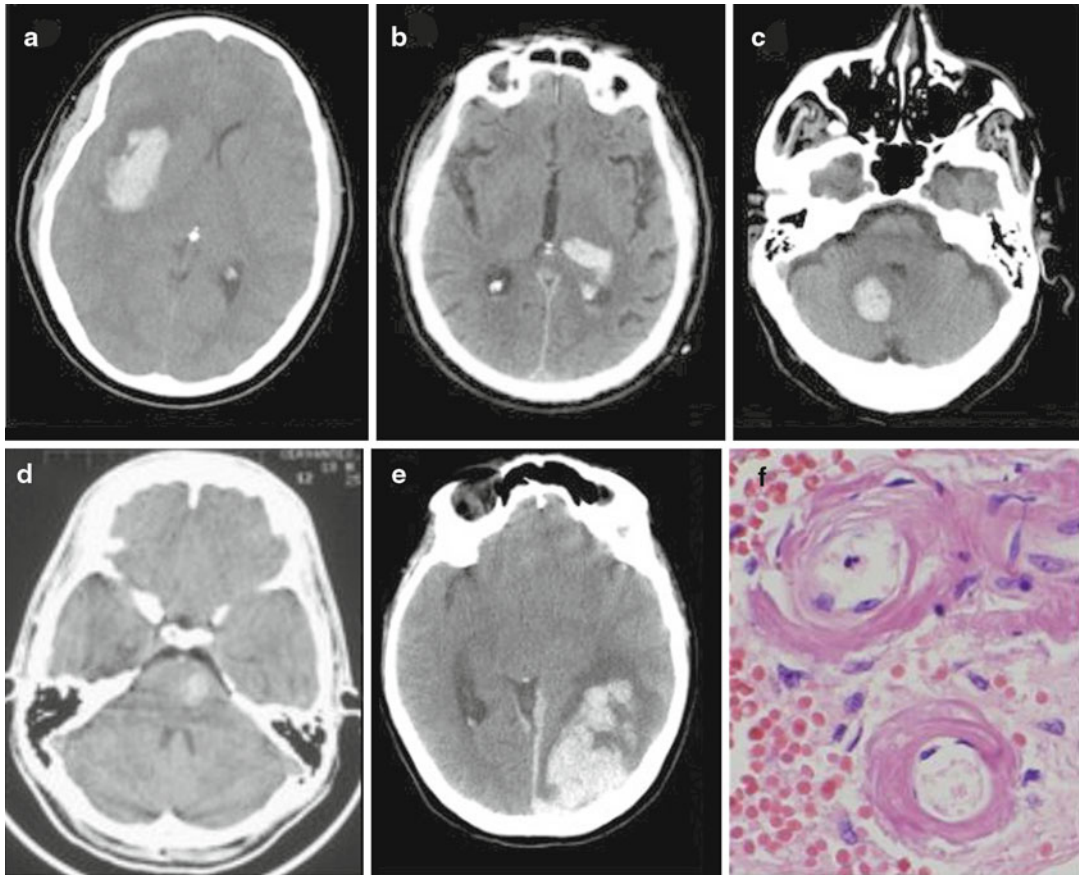

Fig. 9.1 Typical locations for hypertensive intracerebral hemorrhage. (**a**) Putamen, (**b**)Thalamus, (**c**) Cerebellar white matter, (**d**) Pontine tegmentum, (**e**) Lobar white matter. Hematoxylin and eosin photomicrograph (**f**) demonstrating lipohyalinosis of small penetrating arteries that weaken the arterial wall and are the source of typical hypertensive ICH. Photomicrographs provided courtesy of UCSF Neuropathology, Han Lee, M.D., Ph.D., and Andrew W. Bollen, M.D., D.V.M

ICH risk in previous studies. Hypertension imparts a relative risk of ICH on the order of 3.68–5.55, and this increases dramatically with increasing degree of the hypertension [5–7]. Excessive alcohol use also increases the risk of ICH independent of its propensity to cause hypertension (OR 2.12 with >36 g/day of alcohol and OR 4.86 with >100 g/day) [8, 9]. Multiple retrospective and prospective cohort studies have demonstrated that high levels of LDL-C and triglycerides appear to have a protective effect in regard to ICH risk [6, 10, 11]. In a recent retrospective study, lower LDL-C levels (<100 mg/dl versus >100 mg/dl) were correlated with increased risk for mortality in patients presenting with ICH [12]. The SPARCL trial also demonstrated that high-dose atorvastatin in patients with recent stroke may increase the risk of ICH [13, 14]. Conversely, statin use prior to index presentation with ICH is associated with lower initial hematoma volumes but no independent effect on mortality or functional outcome in one prospective observational study [15], while in another study (that did not report nor control for ICH volume), premorbid statin use was associated with better functional outcomes [16]. Nonwhite race has also been consistently associated with higher rates of ICH. While this is likely due in large part to access to care and subsequent poorly controlled hypertension, disparities in ICH rates between blacks and whites (relative risk 1.89 for blacks) cannot be completely explained by socioeconomic factors alone [6, 17]. Hispanic and

Asian patients also have higher rates of ICH, which may be partially explained by higher rates of cerebral vascular anomalies such as cavernous malformations and moyamoya disease [18, 19]. Nonmodifiable risk factors for ICH include age, which imparts a relative risk increase of 1.97 per decade [5, 6], and male gender, which has been variably identified as a risk factor for ICH. Males may be predisposed to deep ICH more than lobar hemorrhages due to their higher rates of hypertension [20].

Although ICH comprises a minority of strokes that occur in the USA, it accounts for a disproportionately large amount of the total morbidity, mortality, and economic burden of stroke. Less than one-third of patients will be functionally independent after experiencing an ICH [21]. The short-term mortality of ICH in most series is approximately 40% and has not improved significantly in recent years despite the growth of neurointensive care. While this is a direct reflection of the absence of any effective proven treatments for ICH, there is also concern that heterogeneity in care and early care limitations may lead to self-fulfilling prophecies of poor outcome [22–25]. Amongst survivors of ICH, health-related quality of life at 90 days is also significantly diminished compared with the general population, and many baseline demographic factors (age, severity of initial neurologic deficit, systolic blood pressure (SBP), ICH volume, deep as opposed to lobar ICH, and early worsening of neurologic status) appear to mediate this relationship [26]. Depression is also prevalent in ICH survivors and may account for this decrement in quality of life in ICH survivors [27]. The economic burden of ICH is tremendous, approaching six billion dollars annually in the USA, and approximately $165,000 per patient/year [28–30].

Pathophysiology

The underlying pathologic process that predisposes to the rupture of small arterioles (<100 μm diameter) in hypertensive ICH has been termed lipohyalinosis. This process is characterized by subintimal fibroblast proliferation, deposition of lipid-filled macrophages, and replacement of smooth muscle cells in the tunica media of the larger vessels with collagen (see Fig. 9.1) [31]. This leads to reduced blood vessel elasticity and increased susceptibility to spontaneous rupture.

The loss of neurologic function due to ICH has classically been ascribed to the tissue destruction caused by the initial hemorrhage as blood transects white matter tracts and destroys neurons. More recently, the importance of damage caused by mechanical effects of the hematoma has been replaced by interest in mechanisms of secondary brain injury. This has been spurred by the observation that many patients deteriorate clinically, without rehemorrhage, in the same time frame in which edema is developing and clot absorption and breakdown are occurring. There is increasing evidence that plasma proteins that are abundant in vasogenic edema and increased by clot resorption are harmful to the brain. Patients with a higher ratio of edema to hematoma volume have been retrospectively shown to have poorer outcomes [32]. Thrombin, as well as hemoglobin and its breakdown products, has been demonstrated to be neurotoxic via glutamate-mediated excitotoxicity, exacerbate acute perihematoma edema, and contribute to disruption of the blood–brain barrier [33]. Additionally, interleukin-1 and matrix metalloproteinases (MMPs) are upregulated in the neurons and astrocytes of the perihematoma region. Perihematoma edema is reduced in experimental models of ICH with both MMP-9 knockout mice and with administration of IL-1 receptor antagonists [34, 35]. Overall, the potentially toxic effects of iron as well as a range of inflammatory mediators have led to the concept of "neurohemoinflammation" as a descriptor for a variety of different pathways which may result in secondary brain injury after ICH. These small molecules and their biochemical signaling pathways, or even iron-chelating agents such as deferoxamine, represent promising targets for future acute ICH therapy which are being investigated in animal and translational research [36–38]. A phase 1 dose-finding safety study is underway to evaluate deferoxamine mesylate in patients with acute

ICH and holds potential to be the first therapeutic intervention to specifically target "neurohemoinflammation" [39, 40].

Concern for perihematoma ischemia has been another area of active investigation regarding mechanisms of ICH-related secondary injury in ICH. Cerebral blood flow studies using SPECT and MRI perfusion and diffusion have attempted to demonstrate a perihematoma penumbra that is at risk for additional injury and neuronal loss due to hypoperfusion [41–43]. The significance of these findings has been called into question by more recent CT perfusion studies that failed to show a penumbra, by PET studies that have found that these areas of "penumbra" may in fact be appropriately perfused in the setting of reduced metabolic activity, and by animal studies which suggest a zone of hypoperfusion without impaired oxygen metabolism [44–46]. A recent PET study demonstrated transient focal increase of glucose metabolism in a subset of patients with ICH that was present at ~3 days postictus but not at 1 nor 7 days [47]; this lends further credence to the hypothesis of an evolving metabolic (but not ischemic) penumbra surrounding an acute hematoma [48].

In the past, ICH has been thought of as a monophasic event with an initial hemorrhage that grew to its maximal size within moments, with rehemorrhage or hematoma expansion as rare events suggestive of coagulopathy or underlying vascular anomaly. However, numerous studies have now demonstrated that hematoma expansion is common early after acute ICH, even in the absence of an underlying lesion or coagulopathy. In a single-center prospective study, substantial hematoma growth, defined as >33% enlargement of the baseline hematoma volume, occurred during the first day in 38% of patients who underwent CT scanning within 3 h of the initial ictus; 26% of patients demonstrated this enlargement within 1 h after initial CT scan [49]. Retrospective studies have found similar rates of rebleeding ranging from 18% to 36% with substantially lower rates of delayed rebleeding beyond 6 h of 2–10% [50–52]. Of note, when examining the placebo group of a phase 2 study of recombinant factor VIIa (rFVIIa) for acute ICH, 73% of patients demonstrated some degree of hematoma expansion over the first day [53]. Because hematoma expansion is an important independent determinant of overall outcome, it is now being strongly considered as a potential target for intervention with hemostatic agents or even aggressive blood pressure control in order to limit hematoma growth [54, 55].

Clinical Presentation and Diagnosis

The clinical presentation of ICH is characterized by the sudden onset of focal neurologic dysfunction that is generally accompanied by severe headache. Prior to the advent of modern CT and MRI neuroimaging, the presence of headache with the ictus was often cited as the defining characteristic of hemorrhagic stroke. However, headache at onset does not reliably distinguish ICH since it occurs in up to 30% of patients with ischemic strokes [56]. Patients with large hemispheric ICH that acts as a mass or who have significant IVH that obstructs cerebrospinal fluid drainage may have profoundly elevated intracranial pressure (ICP) and often present with nausea and vomiting, in addition to focal neurologic deficits that may rapidly progress to herniation and coma. The distinct presentation of coma with pinpoint pupils should immediately alert the practitioner to the possibility of a pontine tegmental hemorrhage. Various baseline clinical and neuroimaging characteristics are predictive of outcome in ICH. These include hematoma volume, Glasgow Coma Scale (GCS) score, IVH, advanced age, infratentorial ICH location, and premorbid cognitive impairment [57–63].

The widespread use of CT scanning has made the diagnosis of ICH relatively straightforward, and it remains the most widely used neuroimaging technique. Acute stroke MRI protocols utilizing susceptibility weighted imaging that exploit the paramagnetic properties of hemoglobin can also accurately identify ICH with very high sensitivity and specificity as compared to CT (Fig. 9.2) [64]. Intracranial vascular imaging with conventional angiography has a high yield in identifying vascular malformations in cases of

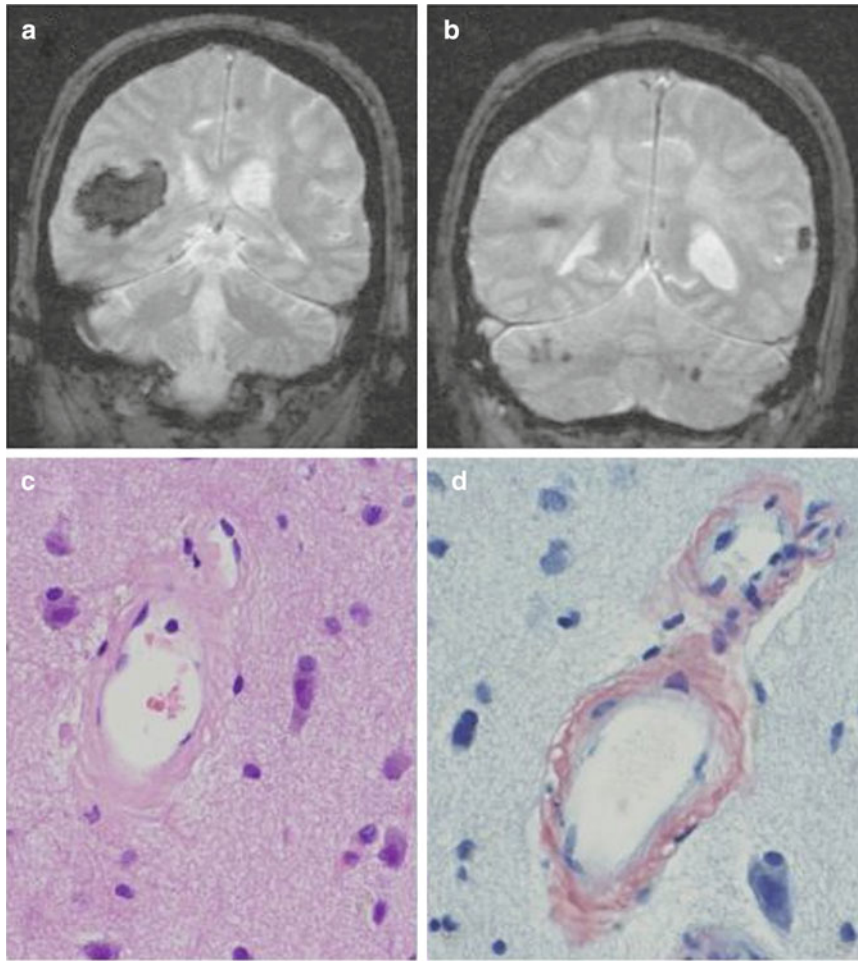

Fig. 9.2 Histopathology and neuroimaging of cerebral amyloid angiopathy (CAA). (**a** and **b**) MRI T2 susceptibility weighted images demonstrating a parieto-occipital lobar hemorrhage with several asymptomatic microhemorrhages scattered throughout the cerebral and cerebellar hemispheres. (**c**) Hematoxylin and eosin photomicrograph of a cerebral arteriole demonstrating medial thickening secondary to amyloid deposition. (**d**) Congo red staining of β-amyloid deposition in the media diagnostic of CAA. Photomicrographs provided courtesy of UCSF Neuropathology, Han Lee, M.D., Ph.D., and Andrew W. Bollen, M.D., D.V.M

ICH in younger patients (age <45), atypical hemorrhage location for hypertension, or if the patient has no history of hypertension [65]. We also advocate for vascular imaging in cases where the hemorrhage appears to be originating in the ventricle as the yield of angiography is quite high in this population [66]. Multislice CT angiography has been proposed as a surrogate for conventional angiography in the investigation of neurovascular disorders [67], but the sensitivity is insufficiently adequate if a vascular malformation is not identified to advocate foregoing conventional angiography [68, 69]. Additionally, in cases of acute ICH, CT angiography with early and delayed image acquisition may be helpful in identifying patients with active contrast extravasation as this is a predictor of hematoma expansion and worsened outcome [70–76]. This type of imaging could theoretically help target interventions toward patients most likely to experience ongoing hematoma expansion, but this has not yet been tested prospectively.

Management of ICH

Blood Pressure

Elevated blood pressure (BP) is extremely common in the setting of acute ICH. Blood pressure management in this setting remains controversial because of concerns over balancing the competing interests of limiting hematoma expansion or rebleeding while avoiding the theoretical risk of secondary ischemic brain injury by hypoperfusing perihematoma brain parenchyma. Studies have conflicted over whether elevated blood pressure predisposes to hematoma expansion after acute ICH [77–79]. However, recent studies have suggested that perihematoma ischemia is unlikely to be a major contributor to ICH-related brain injury in most cases [45, 46, 80]. Even so, there still remains a relative dearth of data to support specific blood pressure goal recommendations and recent American Heart Association/American Stroke Association guidelines for the management of ICH continue to recommend individualized blood pressure goals based upon individual patient characteristics such as presumed etiology of hemorrhage (hypertension versus underlying vascular anomaly), history of chronic hypertension and baseline blood pressure, and known or suspected major vessel arterial stenosis where a significant decline in blood pressure could cause secondary organ damage [81]. These guidelines suggest the following potential approaches: [1] if SBP is >200 mmHg or mean arterial pressure (MAP) >150 mmHg then consider aggressive BP reduction with a continuous intravenous infusion and frequent monitoring of BP and neurologic examination; [2] if SBP is >180 mmHg or MAP is >130 mmHg and there is evidence of or suspicion of elevated ICP, then consider monitoring ICP and reducing BP using intermittent or continuous intravenous medications to keep the cerebral perfusion pressure (CPP) between 60 and 80 mmHg; [3] if SBP is >180 or MAP is >130 and there is no evidence of or suspicion of elevated ICP, then consider a modest reduction of BP (e.g., MAP ≤110 mmHg or target BP ≤160/90 mmHg) using continuous or intermittent IV medications to control BP with frequent monitoring of BP and neurologic examination. While the choice of BP-lowering agent should be individualized based on factors such as heart rate and medical comorbidities (e.g., renal or heart failure), our usual preference is to use agents that preferentially affect cardiac output or are arterial vasodilators, such as bolus doses of intravenous labetalol or continuous intravenous infusion of nicardipine. We try to avoid medications which might cause significant venodilation, such as hydralazine or nitroprusside. Several clinical trials are currently ongoing to test whether aggressive BP treatment limits hematoma expansion and improves clinical outcome after ICH [82, 83]. A recently published multicenter randomized prospective trial demonstrated that intensive lowering of SBP to goal <140 as opposed to SBP to goal <180 decreased the absolute risk of significant hematoma growth (defined as ≥33% of baseline hematoma volume) by 8% without increasing the rate of adverse events [84]; a larger clinical trial based upon these results is underway to test whether this lower SBP goal can improve clinical outcomes [85]. Another recent dose escalation study that was presented at the 2009 International Stroke Conference which examined the tolerability and safety of targeting three different BP goals (SBP 170–200, SBP 140–170, SBP 110–140) using nicardipine infusion found that patients tolerated acute lowering of SBP to the three tiers without significant differences in neurologic deterioration between the three tiers [86].

Coagulopathy

ICH is more frequent in patients treated with anticoagulants and fibrinolytics, and the risk of warfarin-related ICH increases with increasing INR [87, 88]. Warfarin-related ICH is associated with an even higher rate of mortality than ICH in the absence of coagulopathy, and ongoing bleeding in warfarin-related ICH continues for a more prolonged duration [21, 89]. The obvious goal is to urgently reverse the coagulopathy as soon as possible. While this has historically been done

using vitamin K and fresh frozen plasma (FFP), it is now recognized that this approach is suboptimal and often leads to excessively slow correction or failure to correct the coagulopathy entirely [90]. Current guidelines [91] recommend the use of vitamin K 5–10 mg usually administered intravenously by slow push and concurrent treatment with a more rapidly acting reversal agent as it usually takes hours after vitamin K administration for reversal of warfarin-induced coagulopathy [92]. Full warfarin correction usually necessitates the administration of large volumes of FFP and the logistics surrounding cross matching, thawing, and infusion rates make this generally a slower option for correction. Consequently, recent interest has turned to the use of concentrated factor preparations such as prothrombin complex concentrate (PCC) or hemostatic agents such as recombinant factor VIIa. PCC administration generally reverses an elevated INR more rapidly than FFP [93–96] and consequently may be more advantageous in limiting hematoma growth due to ongoing warfarin-related coagulopathy. However, in a study comparing PCC and FFP, there was no difference in hematoma growth between FFP and PCC in patients whose INR was corrected within 2 h [97]. This strongly suggests that it is timing of coagulopathy reversal, not a specific agent that makes the difference. Various current guidelines for warfarin reversal in the setting of life-threatening hemorrhage now emphasize the use of a rapid reversal agent such as PCC or rFVIIa in addition to vitamin K [91, 98, 99].

Hemostatic Agents

The recognition that hematoma expansion worsens outcome and is common even in the absence of coagulopathy has generated significant interest in the potential use of hemostatic agents to limit hematoma growth. Developed as an agent for the treatment of a subset of hemophiliac patients, rFVIIa has now been investigated in a wide range of bleeding disorders in patients with normal coagulation, including ICH [100, 101]. In a phase 2 trial, 399 acute ICH patients who had initial CT diagnosis within 3 h of symptom onset received either placebo or one of three doses of rFVIIa (40, 80, or 160 μg/kg) within 1 h of CT scan. Overall, patients who received rFVIIa had less hematoma expansion and this translated to a lower risk of mortality and improved functional outcome, despite a small increase in thrombotic events such as myocardial infarction [55]. Given these encouraging results, a larger phase 3 trial including 821 patients was conducted with essentially the same inclusion criteria, but comparing placebo and two doses of rFVIIa (20 and 80(μ)g/kg). In this pivotal phase 3 trial, hematoma expansion was once again dramatically reduced by treatment with rFVIIa; however, there was no statistically significant change in the proportion of patients who died or were severely disabled. The total number of thromboembolic events was similar in the three groups, but the number of arterial thromboembolic events was higher in the group treated with 80 μg/kg when compared with placebo. A major critique of the phase 2 trial results is that the placebo group did worse than historical controls, and a major critique of the phase 3 trial results is that there were a larger proportion of patients with IVH in the 20 and 80 μg/kg groups compared with placebo [102]. Post hoc analysis of the phase 3 trial identified a subgroup of patients that might show a robust radiographic and clinical benefit from treatment with rFVIIa (≤70 years of age, ICH volume <60 ml, IVH volume <5 ml, time from onset to treatment ≤2.5 h); this subgroup effect was also confirmed in the phase 2 cohort [103]. Studies are being considered using these clinical or other neuroimaging selection criteria (e.g., CTA contrast extravasation). However, at present, hemostatic therapy cannot be recommended as routine treatment for ICH patients without coagulopathy.

Antiplatelet Agents and ICH

There are conflicting reports as to the role of prior antiplatelet therapy on hematoma expansion and outcome for patients presenting with ICH and the 2007 AHA/ASA ICH guidelines do not address this issue [81, 104–108]. Consequently, there is wide heterogeneity in clinical practice ranging

from practitioners who advocate platelet transfusion in patients with ICH while taking antiplatelet agents, such as aspirin or clopidrogel, to those who advocate the use of laboratory tests for platelet function and to those who choose not to treat. Examination of the placebo group from a neuroprotective ICH study did not demonstrate an association between antiplatelet use and hematoma expansion or outcome [107]. In contrast, recently published work on antiplatelet use and platelet function has suggested that the results of platelet activity assays (but not merely the history of aspirin usage) correlated with occurrence of IVH, a greater ICH score, hematoma growth, and worse outcomes in ICH [109–111]. Given the widespread use of antiplatelet agents, further clarification of the impact of antiplatelet use and platelet dysfunction on ICH occurrence, growth, and outcome is an important future direction.

Intensive Care Management: Intracranial Pressure

Patients with moderate or large ICH or IVH often have increased ICP or hydrocephalus that warrants consideration of treatment. The AHA/ASA guidelines advocate a graded stepwise approach with initial routine use of less invasive measures prior to instituting more invasive measures. These less invasive measures include elevation of the head of the bed to 30°, maintenance of the neck in a neutral position to facilitate jugular venous drainage, and adequate analgesia and sedation. More invasive measures include CSF drainage via an extraventicular drain (EVD) placed directly into the ventricles. An EVD allows continuous measurement of ICP as well as drainage of CSF to treat elevated ICP, but does carry a small risk of hemorrhage or infection. Osmotic agents such as mannitol and hypertonic saline may be used to decrease ICP, but overuse of mannitol may cause hypovolemia, renal failure, and cerebral vasoconstriction. Neuromuscular blockade may also be considered in patients with refractory elevated ICP but is likely associated with an increased risk of infection and critical illness neuromuscular disease. While hyperventilation may rapidly reduce elevated ICP by causing cerebral arterial vasoconstriction, this effect is generally transient (few hours) and reduces cerebral blood flow which might potentially engender secondary brain injury. Thus, we tend to reserve hyperventilation for use as a temporizing measure in preparation for other more definitive medical or surgical treatments. Finally, barbiturate coma may be considered in patients that have failed other therapies but is associated with a significant risk of hypotension and requires continuous electroencephalographic monitoring to titrate effective dosing. Induced hypothermia from 32 to 34°C may also be attempted for a brief period. The use of barbiturate coma and induced hypothermia have not been systematically investigated in ICH and are considered as salvage second-tier therapies at present.

Intensive Care Management: Fever, Glucose, DVT Prophylaxis, Seizure Prophylaxis

Fever is a common occurrence in patients with ICH and increased fever duration is associated with poor outcomes [112]. Thus, fever should be aggressively treated even as appropriate testing for systemic infection is being undertaken. Hyperglycemia on admission is predictive of 14-day and 28-day mortality in patients with ICH [113, 114]. Intensive insulin therapy treatment of hyperglycemia during critical illness has been shown to decrease systemic morbidity and mortality as well as decrease the incidence of critical illness polyneuropathy and seizures [115, 116]. Thus, it is reasonable to vigilantly avoid hyperglycemia in patients with ICH and to institute aggressive approaches to achieve normoglycemia. Even so, randomized trials specifically in patients with ICH have not been performed and concerns have been raised about the possibility of hypoglycemic episodes and their particularly detrimental effects in patients with brain injury [117].

Deep venous thrombosis (DVT) and pulmonary embolism are frequent in patients presenting with ICH, and DVT is diagnosed in approximately

2% of patients during their acute hospitalization [118]. In one study, the combination of compression stockings plus intermittent pneumatic compression decreased the rate of asymptomatic DVT detected at day 10 from 15.9% to 4.7% in patients with ICH [119]. The other intervention study published to date in patients specifically with ICH examined the initiation of low-dose subcutaneous heparin for DVT prophylaxis [120]. Unfractionated heparin 5,000 units three times a day was initiated on the second, fourth, or tenth day following presentation with ICH. There was a statistically significant decrease in the incidence of pulmonary embolism in those patients in whom heparin was started on the second day when compared with the other groups, and importantly there was no increase in intracranial rebleeding. This small study suggests that low-dose subcutaneous heparin can be started as early as the second day in patients who present with ICH and that it may decrease the incidence of pulmonary embolism without profoundly increasing the risk of hematoma expansion or new ICH during hospitalization. In retrospective analysis of patients with ICH at another center, the initiation of the low molecular weight heparin (LMWH) enoxaparin at low dose (20 mg) after the onset of stroke was not associated with hematoma enlargement nor decrease in the number of venous thromboembolic complications [121]. Another study prospectively followed 97 patients with ICH in whom LMWH (enoxaparin or dalteparin at dosing appropriate for DVT prophylaxis) was initiated within 36 h after admission with ICH and found no increased risk of hematoma enlargement [122]. Whether subcutaneous unfractionated heparin or LMWH is superior in patients with ICH has not been specifically tested.

There is a risk of seizures (especially nonconvulsive) in the acute period after ICH, with one study of continuous EEG monitoring (cEEG) in critically ill ICH patients finding that 18 of 63 (28%) had electrographic seizures. In this study, seizures were independently associated with increased midline shift and a trend toward poor outcome [123]. Another prospective cohort study demonstrated that early prophylactic therapy with phenobarbital decreased the risk of developing seizures within the first 30 days in patients with lobar ICH [124]. However, two recent studies have raised concerns over the utility and safety of prophylactic anticonvulsants, specifically phenytoin, in patients with ICH. In a prospective cohort study, phenytoin use was associated with worsened outcome [125]. In a retrospective analysis of the placebo arm of an ICH neuroprotective clinical trial, prophylactic anticonvulsants were associated with worse outcomes without decreasing the rate of early or late seizures [126]. Thus, we do not advocate the use of prophylactic anticonvulsants (especially phenytoin) in patients with ICH, but do use cEEG commonly in ICH patients with unexplained decreased level of consciousness.

Surgery

The decision to undertake surgical evacuation of the hematoma in spontaneous ICH remains controversial and fraught with clinical uncertainty, being still significantly influenced by the bias of practitioners and consultants caring for the patient [127]. Until recently there had only been a few small mostly single-center trials, the preponderance of which did not favor a mandatory approach of craniotomy for evacuation of the hematoma in ICH. These prior trials set the stage for a landmark study entitled the International Surgical Trial in Intracranial Haemorrhage (STICH) [128]. This international, multicenter trial randomized 1,033 patients presenting within 72 h of ictus of spontaneous supratentorial ICH in which the local neurosurgeon decided that there was clinical equipoise about whether or not the patient would benefit from surgery. The patient was randomized to either early surgical intervention (within 24 h of randomization) or initial medical management. The primary outcome measure was death or disability as measured by the extended Glasgow Outcome Score (GOS) at 6 months; different outcome cutpoints were used depending on expected prognosis from the initial hemorrhage [129]. Method of hematoma evacuation and medical management were left to the discretion of local treating physicians and outcomes

were assessed using questionnaires sent to the patients or their families; 506 patients were randomized to early surgical intervention; 530 were randomized to initial medical management, but 26% of these patients ultimately underwent surgery for hematoma evacuation (mostly due to neurologic deterioration) [130]. In an intention-to-treat analysis, early surgery was neither beneficial nor harmful as there was no statistically significant difference in either mortality or functional outcome. Given the design limitations, the results of STICH cannot be used to conclude that surgical evacuation has no role in supratentorial ICH. However, it does demonstrate that a large-scale surgical ICH trial can be successfully completed and that early surgery is unlikely to be a panacea for most patients. Of note, prespecified subgroup analyses identified that patients with hematomas <1 cm from the cortical surface and patients who underwent craniotomy as the surgical procedure had a nonsignificant trend toward benefit with early surgery. Based upon the results of the subgroup analysis, a second international multicenter trial (STICH II) is currently underway to test early hematoma evacuation versus initial conservative management in patients with lobar hematoma 1 cm or less from the cortical surface [131].

There are a number of case series which report that patients with spontaneous cerebellar hemorrhage who present with large cerebellar hematomas (>3 cm in diameter) or with compression of the brain stem or hydrocephalus may still have a favorable outcome with surgical intervention [132, 133]. However, there has not been a prospective randomized trial of surgery for cerebellar ICH analogous to STICH. Even so, cerebellar ICH is generally considered as a potentially surgical lesion by most neurologists and neurosurgeons, especially in patients with obstructive hydrocephalus or clinical deterioration. The 2007 AHA/ASA ICH management guidelines recommend surgical removal of the hematoma as soon as possible in patients with cerebellar hemorrhage >3 cm who are deteriorating neurologically or who have brain stem compression and/or hydrocephalus from ventricular obstruction [81].

A number of minimally invasive surgical alternatives to open craniotomy have also been considered and studied in small case series or pilot clinical trials. These techniques include: simple aspiration of the hematoma [134], mechanical aspiration with a screw and suction technique [135], instillation of a thrombolytic such as urokinase or recombinant tissue plasminogen activator into the hematoma with aspiration of contents [136, 137], and endoscopic aspiration of the hematoma with lavage of the hematoma cavity and photocoagulation of oozing vessels [138]. NIH-sponsored multicenter trials are currently underway comparing catheter-directed t-PA treatment for hematoma evacuation versus conventional medical management for patients presenting with ICH [139] as well as for IVH [140].

Prognostication and the Conundrum of the Self-Fulfilling Prophecy

Recent work has suggested that the use of do-not resuscitate (DNR) orders or other measures of care limitations (such as withdrawal of medical support) early after ICH may independently influence patient outcome even when accounting for other factors [24, 25, 141–143]. Furthermore, studies have found substantial variation in the use of these care limitations across hospitals and physicians [22, 24, 143]. This has raised the concern that perceived poor prognosis very early after ICH might lead to care limitations and death or disability in patients who might otherwise recover if aggressive treatment was instituted. In a single-center retrospective cohort study, Becker and colleagues found that the single most important factor predicting outcome in patients with ICH was the level of care provided; withdrawal of life support negated the predictive value of all other candidate variables to predict outcome [22]. They also found a wide range of prognostication for individual patients amongst physicians of different levels of training and specialty. In another study using discharge records from a large cohort of over 8,000 ICH patients treated at over 200 hospitals in California, the rate at which a hospital used DNR orders within 24 h of hospital admission was an

independent risk factor for death in the individual ICH patient [24]. This suggests that the overall milieu of care in a hospital (aggressive versus nihilistic) may have an important impact on outcome, even in the absence of a proven treatment. Current AHA/ASA ICH guidelines recommend initial aggressive full care and avoidance of new DNR orders within the first 24 h after ICH [81].

Conclusion

Although ICH remains without an approved treatment proven to clearly decrease morbidity and mortality, the last decade has seen notable advances in the understanding of ICH pathophysiology and potential treatments. Recognition of the importance of hematoma expansion and other causes of secondary injury has helped clarify injury mechanisms and suggest new treatments. Major large trials of both medical and surgical therapy for acute ICH have demonstrated the feasibility of clinical trials for ICH treatment, which has lagged behind studies for the interventional treatment of ischemic stroke and SAH. Ongoing basic research has also suggested new targets for treatment that are beginning to be studied in the clinical setting. Given these major advances, optimism about future advances in ICH care is justified.

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Seizures and Status Epilepticus

10

Sandipan Pati and Joseph I. Sirven

Abstract

Seizures are one of the most common neurological emergencies encountered by clinicians. Status epilepticus in particular is one of the most serious forms of seizure emergencies associated with considerable morbidity and mortality. However, much has been learned about the pathophysiology and epidemiology of the condition which has led to a paradigm shift in the definition and management of this condition. This chapter explores the current understanding of seizures with an emphasis on status epilepticus. Epidemiology, etiology, diagnosis, and therapeutic interventions are discussed and protocols for successful management are outlined.

Keywords

Epilepsy • Seizures • Status epilepticus

Introduction

Seizures are one of the most dramatic events that occur in all of medicine, and are immediately perceived by the lay public as an emergency. However, not all seizures are true emergencies. Seizures become emergencies when an individual is either in danger of harming themselves, or alternatively if the seizure continues for a long period of time for which immediate medical attention is necessary.

Seizures account for an estimated 1% to 2% of emergency department visits with higher numbers of emergency department visits among infants and toddlers, males, and African Americans [1]. Although seizures are very common, with 11% of the population having a seizure at some point in their lifetime, epilepsy occurs in only 3% of the population [2]. Thus, most people who have a seizure do not have epilepsy, but rather symptomatic seizures, defined as those caused by well-defined acute insults, such as brain tumor, head injury, and intracranial bleeding. A provoked seizure is caused by an identifiable transient disturbance, such as an electrolyte abnormality (e.g., hypocalcemia).

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Emergency department physicians encounter a number of clinical scenarios involving seizures: new-onset seizures, breakthrough seizures in patients with known epilepsy, and conditions that can mimic seizures. No sign, symptom, or test clearly differentiates a seizure from a nonseizure event (e.g., syncope, pseudoseizure). The clinical history remains the most important tool in distinguishing seizures from their mimickers.

Seizures

When evaluating a patient who has just experienced a seizure, the physician should first verify that the patient has normal vital signs and adequate oxygenation and that there is no further seizure activity. There is no standardized algorithm for the evaluation of every patient with a first seizure. The history should initially focus on determining whether a seizure actually occurred and evaluating the circumstances and characteristics of the event. It should be determined whether there was an aura or a postictal period. Every attempt should be made to interview observers and EMS to obtain a clear description of the seizure to avoid misdiagnosing nonseizure events. It is also essential to conduct a thorough medical review of potential etiologies of seizures. It is important to inquire about sleep deprivation, alcohol consumption, illicit drug use, medical conditions, and prescription medications and any over-the-counter agents, including stimulants and herbals/botanicals. The physical examination should include a thorough neurologic and mental status evaluation. The differential diagnosis of seizures is listed in Table 10.1.

Table 10.1 Differential diagnosis of seizures

Syncope
Migraine with aura
Hypoglycemia
Psychogenic nonepileptic attacks
Panic attacks
Paroxysmal movement disorders
Acute dystonic reactions
Hemifacial spasms
Nonepileptic myoclonus
Sleep disorders
Parasomnias
Cataplexy
Hypnic jerks
Transient ischemic attack
Transient global amnesia

Diagnostic Testing

Diagnostic testing can be helpful in corroborating the diagnosis and establishing an etiology (Table 10.2). Laboratory testing is essential and for the first seizure should include toxicology screening looking for potential agents that may cause seizures, such as cocaine and other stimulants. A complete blood cell count, urinalysis, and chest X-ray are important to assess for infection. Electrolytes also need to be evaluated and should include glucose, sodium, potassium, calcium, and magnesium. Lumbar puncture is indicated in the setting of a seizure and fever to rule out a CNS infection. Neuroimaging studies are a standard of care for epilepsy. Either computed tomography (CT) with contrast or an MRI needs to be performed. A noncontrast CT is not considered a thorough-enough imaging study for patients with seizures. If a patient has a known history of epilepsy and is on antiseizure medications (AEDs), checking serum levels of those medications is helpful to assess compliance as breakthrough seizures often occur in the setting of low concentrations of AEDs. Last but not least, an electroencephalogram is essential to the first seizure workup. The purpose of the EEG is to assess for potential recurrence of seizures if the seizure has stopped and to rule out status epilepticus if the patient has not returned to baseline.

Therapy

If a patient has had a single seizure, therapy with an AED is often not necessary unless there is an obvious structural lesion or overt epileptogenic abnormalities on the EEG, such as a focal or generalized interictal sharp/spike wave. If the patient has more than one seizure, then therapy should

Table 10.2 Diagnostic testing for seizures

Diagnostic test	Assessing for	Comments
Toxicology screen	Positive agents known to cause seizures	Look for stimulant agents such as cocaine, alcohol, and illicit agents
Electrolyte panel	Metabolic derangements	Hypoglycemia, hyponatremia, hypernatremia, hypocalcemia, hypokalemia, hypomagnesemia may all cause seizures
Arterial blood gas	Hypoxia	Hypoxia is a common cause of seizures
Urinalysis	Urinary tract infection	
Chest X-ray	Pulmonary infection	
MRI or CT with contrast	Any structural lesion	The preferred study is MRI of the brain. If a CT, then the study needs to be with contrast
Electroencephalogram	Epileptiform discharges	Must be performed for a first seizure
Serum antiepileptic drug levels	Subtherapeutic levels	Should be assessed only in patients with a history of seizures
Lumbar puncture	Central nervous system infection	Spinal fluid should be analyzed in patients with seizures and fever and in those who are immunocompromised

be initiated. In the emergency department or hospital setting, a benzodiazepine, such as lorazepam or diazepam, is often appropriate for short-term control. If one is looking to initiate an AED with the idea of having the patient remain on the AED for some time, then an intravenous AED may be more appropriate, such as fosphenytoin, phenobarbital, valproic acid, levetiracetam, or lacosamide. Further discussion on the emergency treatment of seizure is discussed in the therapy section of this chapter.

Status Epilepticus

The term "status epilepticus" was first used in 1824 to describe grand mal seizures occurring in rapid succession without complete recovery between convulsions [3]. Research in status epilepticus since then has advanced our understanding from the old concept of "just a cluster of severe seizures" to a self-sustaining unique pathophysiological condition with a potentially poor prognosis.

Definitions

Experts differ in their definition of status epilepticus. It is important to appreciate some of these variations as it has implications for treatment and on epidemiological research. The Epilepsy Foundation of America's Working Group on Status Epilepticus defines status epilepticus as "continuous seizure activity (partial or generalized, convulsive or nonconvulsive) lasting 30 min or more or intermittent seizure activity lasting 30 min or more during which consciousness is not regained" [4]. The term *established status epilepticus* has been applied when these criteria are met. The cutoff time limit at 30 min comes from different scientific sources of evidence:

(a) Experiments in animals have shown status epilepticus becoming self-sustaining within 15–30 min.
(b) Status epilepticus-induced damages become distinct after 30 min of seizure activity.
(c) There is a time-dependent development of pharmacoresistance as seizures progress.

As the prognosis of status epilepticus changes with a delay in starting treatment, it has been suggested that a narrower time window be used for treatment purposes. Thus, a newer terminology—*early or impending status epilepticus*—has been introduced to stress the urgency of starting treatment in all patients who are not in established status epilepticus. "Impending status epilepticus" has been defined as continuous or intermittent seizures lasting more than 5 min, without full recovery of consciousness between seizures [5]. The rationale for 5 min has been adopted in other operational (treatment oriented) definitions and is based on the pathophysiology [6].

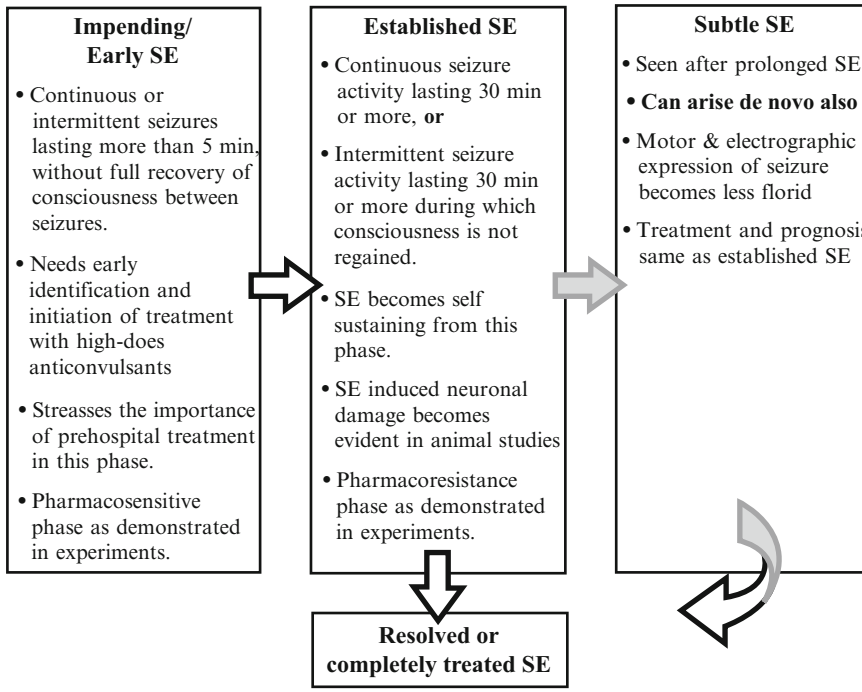

Fig. 10.1 Status epilepticus (SE) can best be understood as a spectrum of three phases each with distinct pathophysiology and unique therapeutic strategies. The *arrows* demonstrate the typical timeline in which these phases manifest. SE typically begins in an early phase characterized by discrete seizures without intervening recovery. It then progresses to established SE which implies at least 30 min of seizures without recovery. After established SE, the condition can either resolve after treatment or it can lead to subtle or refractory SE. Refractory SE can either resolve with treatment or continue unabated until death

Subtle status epilepticus is a term suggested by Treiman to emphasize that during prolonged status epilepticus both the motor and electroencephalographic expression of seizures become less florid, yet the prognostic and therapeutic implications of that stage are still those of convulsive status epilepticus [7]. Sometimes subtle status epilepticus may appear de novo after a severe insult to the brain. The greater the degree of encephalopathy present, the more subtle is the convulsive activity.

Lowenstein et al. [8] proposed that continuous, generalized convulsive seizures be defined as status epilepticus when they last more than 5 min, and when two or more seizures occur during which the patient does not return to baseline consciousness. Generalized convulsive status epilepticus (GCSE) has been conceptualized into three distinct phases to capture the transition from isolated seizures to status epilepticus and in the development of time-dependent pharmacoresistance. Figure 10.1 illustrates this theoretical construct of status.

Status epilepticus has been classified in many ways based on either the symptomatology of the seizures, epilepsy syndromes, or a treatment oriented scheme. The World Health Organization and the ILAE has classified status epilepticus on the basis of clinical semiology and electrographic classification (Table 10.3). Overt GCSE is easily recognized as recurrent generalized convulsions without full recovery of neurologic function between seizures.

The term *partly treated status epilepticus* refers to the cessation of clinical seizures or only subtle symptoms, but the continuance of electrographic seizures. Epidemiological studies suggest 10% of patients treated for status epilepticus remain in this group. Experimental studies suggest uncontrolled firing alone can kill neurons.

Table 10.3 Classification of status epilepticus (as per WHO and ILAE) [1]

Generalized SE	Partial or focal SE
Convulsive	Simple partial attacks
	Partial elementary
Tonic–clonic	Motor
Tonic	Sensory
Clonic	Somatomotor
Myoclonic	Dysphasic
Nonconvulsive	Continuous partial epilepsy
Absence status	(Epilepsia partialis continua)
	Complex partial attacks
Unilateral SE: hemiclonic SE	
Nonclassifiable SE	
Erratic SE	

Refractory status epilepticus is defined as seizures lasting longer than 2 h or seizures recurring at a rate of two or more episodes per hour without recovery to baseline between seizures, despite treatment with conventional antiepileptic drugs (AEDs) [9]. However, in clinical practice, status epilepticus is often considered to be refractory in any patient who has not responded to first-line AEDs. The likelihood of response to another add-on AED decreases with the failure of the first AED.

Epidemiology

Status epilepticus epidemiological studies are difficult to assess as status epilepticus occurs not only in people with epilepsy, but also in individuals with acute systemic and neurologic illness. Nevertheless a handful of retrospective and prospective epidemiological studies conducted in different communities have contributed to our understanding of status epilepticus. The annual estimates of status epilepticus in the UK, the USA, and worldwide are approximately 14,000, 150,000, and three million cases, respectively.

The age-specific incidence curve of status epilepticus is U-shaped as is the incidence of recurrence of status epilepticus. The highest incidence occurs in young children (less than 1 year old, approx 160/100,000 population) and the elderly (greater than 85 years, approx 111/100,000 population). Some studies have demonstrated a higher incidence of status epilepticus among males compared to females with a ratio of 1.5–2:1 [10]. The higher incidence of status epilepticus among the elderly is worrisome because concurrent medical conditions are more frequent and management is often complicated and thus the prognosis worse. The estimated cost of status epilepticus in the USA is $4 billion per year and more than $90 billion worldwide.

The risk of recurrent status epilepticus is highest among individuals who have already experienced one episode of status epilepticus when compared with those with seizures who have never experienced status epilepticus. In one series, recurrence was much more common during the first year of life. Recurrence rates in the pediatric, adult, and elderly population were 35%, 7%, and 10%. Overall 13% of patients experienced repeat episodes of status epilepticus [11]. Status epilepticus recurrence is highest (about 80%) in those with progressive symptomatic status epilepticus [12, 13].

Approximately, one-fifth to one-third of all status epilepticus cases are reported to be refractory status epilepticus, which means around 50,000–60,000 per year alone in the USA [14]. Refractory status epilepticus is associated with an increased length of hospital stay and functional disability. Nonconvulsive status epilepticus (NCSE) and focal motor seizures at onset are risk factors for refractory status epilepticus.

In the Richmond study, partial status epilepticus with secondary generalization is the most common seizure type in both children and adults, while generalized tonic–clonic status epilepticus is the major form of status epilepticus as the final seizure type. Approximately 69% of adults with status epilepticus and 64% of children with status epilepticus presented with partial status epilepticus as the initial seizure type. When seizures did not secondarily generalize, simple partial status epilepticus was more common than partial complex status epilepticus in both children and adults [11].

Etiology

The profile of etiologic risk factors is different in children and adults. In adults the most common causes of status epilepticus are lower antiepileptic drug levels in individuals with epilepsy (34%), remote symptomatic causes (24%), and acute or remote cerebrovascular disease (22%). In children the commonest causes of status epilepticus are infection with fever (52%), remote symptomatic causes (39%), and lower antiepileptic drug levels in individuals with epilepsy (21%). Etiologies in different age groups are further detailed in Table 10.4 [15].

One notable point with regards to etiology is that a significant number of patients with no history of epilepsy can present with status epilepticus. A study based on a twin registry at the Virginia Commonwealth University suggested the role for genetics in status epilepticus [16].

Pathophysiology

Status epilepticus occurs when there is a failure of the mechanism that terminates a single seizure thereby leading to prolonged or multiple self-sustaining seizures. Understanding the mechanisms involved in the transformation from isolated seizures to self-sustaining status epilepticus might help us to prevent intractable status epilepticus and the consequences of status epilepticus, which are brain damage, and epileptogenesis. There is no proof that seizures become self-sustaining in human beings, but studies in experimental animals have theorized some possibilities. Three important basic mechanisms are associated with status epilepticus:

Table 10.4 Etiology of status epilepticus in different age groups

Etiology in pediatric age group	Etiology in adult
Infection with fever (52%)	Lower antiepileptic drug level (34%)
Remote symptomatic causes (39%)	Remote symptomatic causes (24%)
Lower antiepileptic drug levels (21%)	Cerebrovascular disease (22%)
Cerebrovascular accident	Metabolic
Metabolic	Hypoxia
Idiopathic	Alcohol-related
Hypoxia	Tumor
Anoxia	Systemic infection with fever
CNS infection	Anoxia
Drug overdose	Trauma
Trauma	Drug overdose
Tumor	CNS infection
Hemorrhage	Idiopathic
	Hemorrhage

1. *From isolated seizure to status epilepticus*: Experimental hypotheses that explain the transition of isolated seizure to status epilepticus include marked changes in ionic channels (shift of sodium, chloride, calcium), adenosine formation/release, electrical synchronization, and failure of GABA-mediated inhibition [17]. Neurologic insults either lower the seizure threshold or result in excessive excitation or failure in inhibitory mechanisms. Some of the mechanisms which are responsible for termination of seizures are blockade of N-methyl-D-aspartate (NMDA) channels by magnesium, activation of K+ conductances and thus repolarization of neurons and neuropeptide Y [18], and change in GABAA receptors. Failure in either of these terminating mechanisms can lead to status epilepticus. In addition, the activation of the NMDA receptor by the excitatory neurotransmitter glutamate may be required for the propagation of seizure activity [19].

   Once self-sustaining status epilepticus is established, it is maintained by underlying changes that do not depend on continuous seizures activity and it is easily stopped by only a few drugs, all of which directly or indirectly inhibit glutamatergic neurotransmission [20]. Maladaptive changes in the form of increased expression of proconvulsive neuropeptides (substance P, neurokinin B) and depletion of inhibitory neuropeptides (neuropeptide Y, galanin, somatostatin) that contribute to a state of raised excitability have been described.
2. *Time-dependent pharmacoresistance*: Another important finding in experimental animals is the progressive time-dependent development of pharmacoresistance. This has been attributed to an alteration in the functional properties of

GABA receptors present in the hippocampal dentate granule cells. Kapur and MacDonald showed that the anticonvulsant potency of benzodiazepines can decrease by 20 times within 30 min of self-sustaining status epilepticus [21]. Mazarati and Wasterlain showed a mechanistic shift from inadequate GABAergic inhibitory receptor-mediated transmission to excessive NMDA excitatory receptor-mediated transmission in an animal model [22]. Anticonvulsants like phenytoin also lose potency, but more slowly. Translocation of calmodulin from the membrane to the cytosol has been associated with phenytoin resistance [23]. There is no evidence of development of pharmacoresistance in human beings, although epidemiological studies suggest early treatment is much more effective than late treatment.

3. *Seizure-induced neuronal injury and death*: Continuous seizures, even in the absence of convulsive activity, cause neuronal loss and this cell death is the result of excessive neuronal firing through excitotoxic mechanisms [24]. Additionally, apoptosis is likely to play a role in cell death during status epilepticus [25]. It is important to note that in experiments where systemic factors are controlled, there is still damage to the brain. Decreased neuronal density in the hippocampi of patients who died from status epilepticus has been reported [26]. In animal studies, neuronal damage has been demonstrated in the substantia nigra pars reticularis after 30 min of seizure activity and in the third and fourth layer of the cerebral cortex and CA-1, CA-4 sublayers of the hippocampus after 45–60 min of seizure [27]. Neuron-specific enolase, a marker of neuronal death, is increased in the serum of patients after status epilepticus [28]. Given the probability of cerebral injury, it is imperative for the clinician to recognize and treat status epilepticus expeditiously.

Systemic Changes with Status Epilepticus and Complications

The systemic effects of status epilepticus are a consequence of the massive catecholamine release that occurs together with excessive muscular activity. Lothman divided these progressive changes into two phases: the first phase lasts up to 30 min after seizure initiation; the second phase continues after the initial 30 min (Fig. 10.2) [29]. As a result of sympathetic overdrive, the body responds to GCSE with both systemic and cerebral complications. Systemic complications are more limited with NCSE. It is important to anticipate the possible complications of status

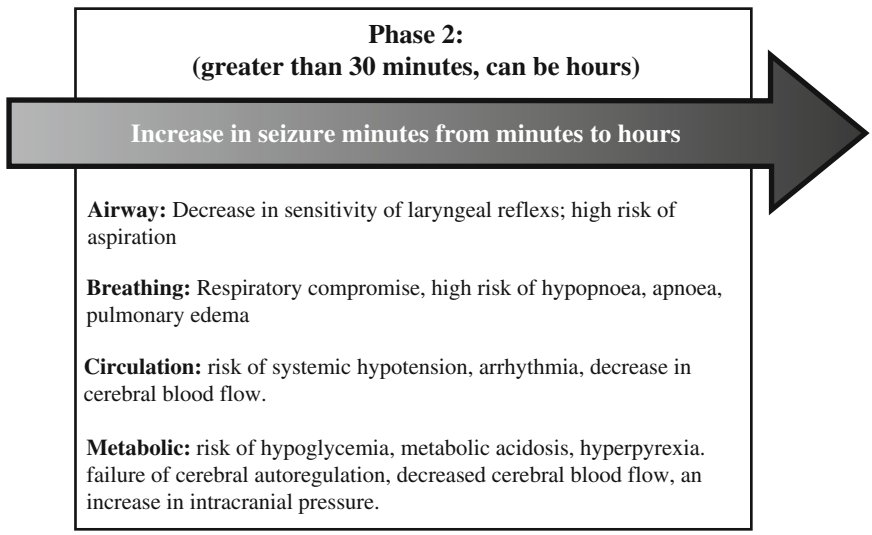

Fig. 10.2 The systemic consequences of persistent seizures are outlined below. The ABCs of critical care must be managed during SE

Table 10.5 Systemic and CNS complications of status epilepticus

System	Complications
Cardiovascular	Arrhythmias Arrest Tachycardia, bradycardia Congestive heart failure Hypertension, hypotension
Respiratory	Apnea Pulmonary edema Adult respiratory distress syndrome Nosocomial infection Aspiration Laryngeal spasm Respiratory acidosis Pulmonary embolus
Central nervous system	Cerebral edema Carbon dioxide narcosis Cerebral hypoxia Cerebral hemorrhage
Metabolic	Metabolic acidosis Hyperkalemia Hyponatremia Hypo/hyperglycemia Dehydration
Renal	Renal tubular acidosis Acute nephritic syndrome Oliguria/anuria Uremia Rhabdomyolysis Myoglobinuria
Endocrine	Hypopituitarism Elevated prolactin Elevated vasopressin Elevated plasma cortisol Weight loss
Miscellaneous	Disseminated intravascular clotting Loss of intestinal mobility Pandysautonomia Multiple organ dysfunction syndrome Fractures

epilepticus as they are the fundamental reason for the high morbidity and mortality associated with status epilepticus. There are numerous complications secondary to status epilepticus as detailed in Table 10.5 [30].

Clinical Presentation

For practical purposes status epilepticus can be subclassified into convulsive status (focal or generalized) and nonconvulsive status (complex partial attacks or absence seizures) based on the clinical manifestations of the seizure activity.

Convulsive Status Epilepticus

GCSE is the most common and serious form of status epilepticus. The evolution of this form of status epilepticus from overt to subtle GCSE has been well described in experimental and clinical studies. Clinical features of subtle GCSE are profound coma with convulsive activity limited to nystagmoid movement of the eyes or intermittent brief clonic twitches of the extremities or trunk, and bilateral ictal discharges on the EEG [31]. *Generalized myoclonic status epilepticus* is predominantly seen in children. Convulsive *simple partial status epilepticus (*i.e.*, epilepsia partialis continua)* is characterized by repeated partial motor seizures, preserved consciousness, and preserved neurovegetative regulations. Repeated clonic jerks with localization depending on the localization of the epileptogenic lesion in the primary motor cortex are the cardinal clinical feature [32].

Nonconvulsive Status Epilepticus

The definition and clinical features of NCSE are more heterogeneous and controversial. The semiological spectrum of NCSE ranges from negative symptoms (coma, catatonia, aphasia, confusion) to positive symptoms (agitation, automatisms, delirium, delusion, psychosis) [33]. Apart from absence status epilepticus and complex partial status epilepticus (CPSE), the term NCSE has often been applied to patients who are severely obtunded or comatose with minimal or no motor movements. Thus definitions of NCSE should include: (1) unequivocal electrographic seizure activity, (2) periodic epileptiform discharges or rhythmic discharges with clinical seizure activity, and (3) rhythmic discharges with either clinical or electrographic response to treatment [34].

In a series of 570 critically ill patients monitored to detect subclinical seizures or for unexplained depressed level of consciousness, 18% were having nonconvulsive seizures and 10% were in NCSE [35]. *Typical absence status*

epilepticus involves prolonged absence attacks with continuous or discontinuous 3-Hz spike and wave occurring in patients with primary generalized epilepsy. Isolated impairment of consciousness, at times with subtle jerks of the eyelids, is the essential symptom. The term *complex partial status epilepticus* implies a prolonged epileptic episode in which focal fluctuating or frequently recurring electrographic epileptic discharges, arising in temporal or extra temporal regions, result in a confusional state with variable clinical symptoms. Clinical features include clouding of consciousness, various automatisms (oroalimentary, gestural), and language disturbances. *Electrical status epilepticus during sleep* is characterized by spike-and-wave discharges in 85–100% of nonrapid eye movement (REM) sleep. This is associated with certain epilepsy syndromes such as Landau–Kleffner and Lennox–Gastaut syndromes [36].

Investigations in Patients with Status Epilepticus

The diagnosis of status epilepticus is often clinical. Investigations are done to find the etiology of the status epilepticus, to define the type of status epilepticus syndrome, and to differentiate from other acute neurologic conditions that can simulate complex partial status epilepticus (intoxications, encephalitis, metabolic disorders, pseudostatus). These diagnostic assessments are important but should not delay treatment. A summary of the diagnostic tests obtained from different guidelines and systematic review is presented in Table 10.6.

Management

Management of status epilepticus is divided into three categories: prehospital management, management in the acute setting (emergency department and intensive care unit), and management of prolonged status epilepticus, which is predominantly performed in the intensive care unit.

Prehospital Management [37]

The result of early treatment of status epilepticus in the ambulance, home, or at a care facility is that seizures are more likely to respond and that overall treatment costs and outcome may be improved. Rectal diazepam is safe and effective in both adults and children in the prehospital care of patients with frequent seizures. The intravenous administration of lorazepam (2 mg) or diazepam (5 mg) by paramedics is reasonably safe and is the best documented treatment in the prehospital setting. In children, nasal midazolam is effective in terminating seizures [38]. The intramuscular administration of lorazepam seems to be safe and fast acting in adults and the oral administration of midazolam is effective in adults with disabilities (level C evidence) and in children (level C evidence).

Management in the Emergency Department and Intensive Care Unit

Airway, arterial blood gas monitoring, and ECG and blood pressure monitoring are vital during the course of treatment. The presence of hypoxia and respiratory acidosis is an indication for intubation in most cases. In one-third of adults in status epilepticus, arterial pH falls below 7, primarily due to lactic acidosis from skeletal muscle convulsive activity. Respiratory acidosis responds well to oxygen and control of convulsive activity. Maintain cerebral perfusion pressure (CPP) above 60 mmHg. The systolic pressure should be maintained above 120 mm Hg if possible, and should not be allowed to fall below 90 mm Hg, even if this requires the use of vasopressors. Prevent cerebral edema as much as possible with attention to brain tissue oxygenation and electrolyte balance. Cerebral edema can be treated with a 10% to 20% mannitol infusion (0.5–1.5 g/kg/dose, in 15–30 min, after ruling out the presence of cerebral hemorrhage). Should this fail, assisted respiration can be considered with hyperventilation and IV pentobarbital. Corticosteroids do not seem to be effective for treating cerebral edema

Table 10.6 Diagnostic tests in patient with status epilepticus

Tests	Indication	Comments
Electrolytes (e.g., sodium, calcium, magnesium, glucose)	They are performed according to suspected etiology and patient history	Abnormalities averaged 6% in children
Serum AED level	In children and probably also in adults who are treated chronically with AEDs (level B)	Low levels of AEDs are found in up to 32% of epileptics with SE
Toxicology study	Performed whenever there is no evident etiology at the first examination (level C)	Frequency of ingestion as a diagnosis in children was at least 3.6%. Both blood and urine should be sent. Routine test as "triage" discouraged
Blood culture	Insufficient data to support or refute whether blood cultures should be done on a routine basis (level U evidence). Perform if there is a strong suspicion of systemic infection or in cases of febrile SE in infants	The yield of blood culture was 2.5% in children with SE
Lumbar puncture	Insufficient data to support or refute whether LP should be done on a routine basis (level U evidence). However it is always necessary in neonatal SE	The yield was 12% in children with febrile SE and bacterial meningitis. Twenty percent of the patients may have nonspecific reactive pleocytosis in the CSF after SE
Cranial CT scan	Considered when there are clinical indications or if the etiology is unknown (level C). It is essential in cases of SE involving partial attacks and in patients with evidence of focality in the first neurologic assessment. Better than MRI in emergency as it detects almost all structural pathologies which require emergency neurosurgical interventions	Insufficient evidence to support or refute recommending routine neuroimaging (level U). Complex partial SE, simple partial SE, and generalized convulsive SE requires scan. Contrast-enhanced CT is necessary when non-contrast-enhanced CT suggests vascular anomaly or isodense subdural hematoma
Cerebral MRI	Insufficient evidence to support or refute recommending routine neuroimaging (level U). It should be performed to supplement the information provided by the cranial CT scan, and in all cases of cryptogenic diagnosis with normal cranial CT results	Better than CT in nonemergency for cerebral structural evaluation. Diagnostic yield is high
Electroencephalography	Indicated to define the electroclinical type of SE, guide to maintenance antiepileptic treatment, and in defining a possible evolving epileptic syndrome. It is indicated when nonconvulsive or subtle SE is suspected and in patients who have received a long-acting paralytic agent or who are in drug-induced coma (level C)	Generally not an urgent test, unless there are doubts concerning the origin of the paroxysmal episode (nonepileptic paroxysmal disorders or pseudo status)
Genetic and congenital metabolic error studies	Insufficient evidence to support or refute whether such studies should be done routinely (level U). In children, metabolic studies recommended when the initial evaluation reveals no etiology and there is a preceding history suggestive of a metabolic disorder	Nonconvulsive SE has been associated with ring chromosome 20 syndrome

Classification of recommendations (as from American Academy of Neurology) [1].
Level A rating requires at least two consistent Class I studies.
Level B rating requires at least one Class I study or at least two consistent Class II studies.
Level C rating requires at least one Class II study or two consistent Class III studies.
Level U means data inadequate or conflicting; given current knowledge, test is unproven.
Summarized from American Academy of Neurology practice parameter guideline and review article by Perias et al. [1].

due to status epilepticus. Hyperglycemia, which is secondary to catecholamine release, does not need correction in most cases, and is not as harmful to the brain during status epilepticus as in ischemia, as circulation can carry lactate out of the brain. Some studies suggest mild acidosis is an anticonvulsant and neuroprotective [39]. Hypoglycemia in adults is treated by an initial bolus of 50 mL of 50% glucose after the IV administration of 100 mg of thiamine (to prevent the possible development of Wernicke encephalopathy). In children, an initial bolus of 2 mL/kg of 25% glucose is recommended.

Pharmacotherapy of Status Epilepticus

Intravenous benzodiazepines, which work through enhancing gamma-aminobutyric acid (GABA) inhibition of repetitive neuronal firing, are the first-choice antiepileptic drug, with an efficacy of at least 79% in stopping the seizure. Phenytoin and valproate are considered as second line, whereas barbiturates and lidocaine are some of the third-line drugs. Detailed descriptions of these drugs are provided in Table 10.7 [40]. There are many protocols/drug regimens for the management of status epilepticus. Figure 10.3 is one of them [41]. More than the use of specific drug or a specific drug order, the most important factor in status epilepticus termination is the rapid use of effective drugs in adequate doses, based on estimated weights and mg/kg requirements.

Some of the less commonly used antiepileptic drugs which have been tried in status epilepticus, especially refractory status epilepticus, are:

(a) *Magnesium* [42]: useful in seizures due to eclampsia and hypomagnesemia. In eclampsia target level of serum magnesium is 3.5–6.0 mEq/L. This level is achieved by infusion of 5 g of magnesium sulfate over 5–30 min, followed by 1 g/h of continuous infusion.
(b) *Nonnarcotic anesthetics*: Isoflurane, etomidate, and ketamine have been used in treating refractory SE. Clinical trials with these are limited. Etomidate has a high risk of adrenal insufficiency due to acute hemorrhage of the adrenal glands [43], whereas there is considerable risk of respiratory depression, apnea, and laryngospasm with ketamine [44].
(c) *Pyridoxine*: This drug has been used in refractory status epilepticus in children under 3 years of age with a history of chronic epilepsy or in established neonatal status epilepticus or refractory status epilepticus in infants [45].
(d) *Newer antiepileptics*: Topiramate [46] and levetiracetam [47] has been used for the treatment of refractory status epilepticus.

Some of the antiepileptic drugs used in specific types of status epilepticus are summarized below [48]:

(a) *Generalized convulsive status epilepticus*: Intravenous lorazepam or phenobarbital or diazepam–phenytoin combinations are acceptable initial treatments. In 20–35% of patients, initial therapy will fail. Fosphenytoin or phenytoin is an attractive second choice and general anesthesia is a third choice.
(b) *Typical absence status epilepticus (NCSE)*: intravenous or oral benzodiazepines as initial treatment.
(c) *Complex partial status epilepticus (NCSE)*: oral, rectal, or intravenous benzodiazepines as initial treatment (protocol similar to GCSE).
(d) *NCSE in coma*: intravenous benzodiazepines and phenytoin (fosphenytoin) or phenobarbital together with anesthetic agents.
(e) *Atypical absence status epilepticus (NCSE)*: oral or intravenous valproic acid.
(f) *Electrical status epilepticus during sleep*: oral clobazam.
(g) *Myoclonic status (following hypoxia, in nonprogressive encephalopathies)*: clonazepam, piracetam.
(h) *Status epilepticus in neonates*: Phenobarbital is the most frequently used in neonatal seizures.

Management of Refractory Status Epilepticus

Refractory status epilepticus requires aggressive treatment; however, optimal treatment has not been defined. Refractory status epilepticus is best managed with a multidisciplinary team in the

Table 10.7 Summary of some of the common drugs used in the treatment of status epilepticus

Generic name/common route of administration	Loading dose	Maintenance dose	Half-life/time to peak concentration	Comments
First-line drugs	0.15 mg/kg	Not typically used	28–54 h/peaks	Diazepam gel peaks in 45–90 min, but therapeutic level is maintained for 8 h compared to 2 h for IV diazepam
Diazepam/IV	at 5 mg/min	as maintenance therapy	in 2–30 min	
Lorazepam/IV	0.1 mg/kg	Repeat to max	8–25 h/peaks	Longer-acting anticonvulsant effect than diazepam. 26% hypotension and less than 20% respiratory depression in VA cooperative study (Treiman et al.)
Midazolam/IV	at 2 mg/min	of 2 mg/min	in 30–120 min	
Clonazepam/IV	0.2 mg/kg by slow IV push	0.75–10 mg/kg/min for 12–24 h	3 h/peaks in 30 min	Low peak concentration due to poor bioavailability, use in acute seizure not recommended. Respiratory depression noted. Can be given IM
	0.05–0.1 mg/kg		18–39 h/peaks in 10–30 min	Main disadvantages are bronchorrhea/bronchoplegia. Limited clinical experience
Second-line drugs	20 mg/kg at 50 mg/kg	<50 mg/min	24 h (wide variation)/	Heart rate, blood pressure, and the ECG should always be monitored because of the risk of cardiac arrhythmia and hypotension. It precipitates when mixed with most parenteral solutions except physiologic saline solution, and often causes phlebitis at the infusion site
Phenytoin/IV	(max of 30 mg/kg)	(reduce to 0.3 mg/kg/min	peaks after 15 min	
Fosphenytoin/IV	20 mg/kg at 50 mg/kg	in elderly, critically ill,	24 h (wide variation)/	
Valproate/IV	(max of 30 mg/kg)	and liver disease patients)	peaks in 20 min	
Levetiracetam/IV	phenytoin equivalents		15 h/peaks in 20 min	Can be given orally
Lacosamide/IV	20–40 mg/kg	<50 mg/min phenytoin	12 h	High price when compared with PHT, does not produce respiratory depression or alter consciousness
	1,500–3,000 mg	equivalents	12 h	
	over 25 min	4–8 mg/kg tid		Not to be used in children with acute liver disease or patients with inherited metabolic disorders
	200 mg over	1,500 mg PO bid		Not FDA approved for status
	30–60 min	200 mg PO bid		Not FDA approved for status. PR prolongation on EKG is possible
Third-line drugs	20 mg/kg at	2–4 mg/kg qd	96 h/peaks in 3–60 min	Longest half-life which is influenced by age; neonates have the highest. In VA study, reported side effects were hypotension (34.1%), hypoventilation (13.2%), and cardiac rhythm disturbances (3.3%)
Phenobarbital/IV	50–75 mg/min	20 mg/kg/h	6 h/peaks immediately	
Paraldehyde/IV, rectal, nasogastric tube	(max of 30 mg/kg)	(0.4 mL/kg/h	with IV, with other	
	100–200 mg/kg	of a 5% solution)	route takes 30–120 min	Bioavailability of rectal route is 80%. The IV solution must be 5% or less because of reduced solubility (7.8%) at body temperature. Pulmonary edema, pulmonary hemorrhage, and right heart failure are some of the side effects
Lidocaine/IV	diluted to 5%	0.6–9.0 mg/kg/h	2 h/peaks within	
Propofol/IV	solution	(max 300 mg/h)	4–8 min	
Pentobarbital/IV	1.5–2 mg/kg	2–15 mg/kg/h	2 h/peaks in 5 min	Dose-dependent CNS depression. Can cause bradycardia and hypotension
Thiopental/IV	1–2 mg/kg by slow IV push	0.5–1 mg/kg/h	10–20 h	Monitoring with continuous EEG and blood pressure in ICU setting recommended. Bradycardia and hypotension are frequent side effects
	10–15 mg/kg	3–5 mg/kg/h	12–36 h	Effects monitored by regular EEGs, measuring the frequency of paroxysm-suppression intervals, and BP monitoring. Hypotension and respiratory depression common
	100–200 mg			Induces coma requiring artificial respiration in an ICU. Use is associated with a high morbidity and mortality rate and should therefore only be used for 24–48 h

	Adults	Children	General steps
Impending SE (out of hospital treatment) **5 mins**	• Diazepam 0.2mg / kg rectally (>12 yrs) approx 10-15 mg **or** • IV lorazepam 2 mg, may repeat once **or** • IV diazepam 5 mg, may repeat once	• Diazepam 0.5 mg/kg rectally (2-5 yrs) 0.3 mg/kg rectally (6-11 yrs) **or** • IV lorazepam 0.2mg/kg, **or** • IV diazepam 0.5 mg/kg @ 2mg/min may repeat once	• Lateral prone position • Clear airway • Remove harmful things from nearby
Established SE (in emergency room) **5-30 mins**	• Intravenous midazolam 0.2 mg/kg bolus 0.05 mg/kg/h **or** • Intravenous lorazepam up to 0.1 mg/kg **or** • Intravenous diazepam up to 0.25–0.4 mg/kg **and** • IV fosphenytoin 15–18 mg PE/kg at max.@ of 150 mg PE/min **or** • IV phenytoin 15–18 mg/kg at max.rate of 50 mg/min • Consider valproate 25mg/kg IV in pts.normally taking valproate and who may be subtherapeutic or if seizure coutinues even after phenytoin infusion	• IV lorazepam 0.1 mg/kg **or** • IV diazepam 0.3 mg/kg **and** • IV fosphenytoin 15–18 mg PE/kg at max.@ of 150 mg PE/min **or** • IV phenytoin 15–18 mg/kg at max. rate of 50 mg/min • If seizure still continues onsider IV phenobarbital 15–20 mg/kg at max. rate of 100 mg/min	• Airway, oxygen, Cardiorespiratory function monitor • IV access, ECG, SpO2 monitor. • IV glucose, thiamine • IV pyridoxine 100 mg for children < 2 yrs of age. • Send blood for initial investigations, • AED level when required. • Consider imaging after stabilizing the patient • EEG specially if pseudostatus epilepticus is suspected.
Refractory SE (intensive care unit) **>30 mins**	• Propofol loading 2–5 mg/kg (IV infusion 2–10 mg/kg/h) **or** • Midazolam loading 0.2 mg/kg (IV infusion 0.1–2 mg/kg/h) **or** • Pentobarbital loading up to 10 mg/kg 25 mg/min (IV infusion 0.5–2 mg/kg/) **If seizure continues** • Topiramate 150–750 mg bid via NGT **If still continues** • Consider inhalation anesthesia or ketamine • Consider surgical intervention		• Intensive care; ventilatory and haemodynamic treatment • Increased intracranial pressure; measure and treat if sings • Continuous EEG monitoring; electrographic sezures, depth of anaesthesia • Optimise maintenance AED treatment

Fig. 10.3 Treatment protocol for status epilepticus in adults and children, time calculated from the onset of the seizure. Adapted from three different sources: Chen and Wasterlain [6]; Alldredge et al. [37]; Lowenstein et al. [8]

intensive care unit with continuous monitoring of hemodynamic parameters and EEG. Without EEG the response to AED treatment is difficult to verify, as subclinical, electrographic seizure activity can be detected in up to 48% of patients after the cessation of clinical symptoms of GCSE. However, it should be noted that a delay in obtaining an EEG should not withhold treatment. Complications should be aggressively managed. Continuous intravenous anesthetics (midazolam, propofol, thiopental, pentobarbital) are commonly used in refractory GCSE. In a meta-analysis of continuous intravenous anesthetics, the overall rates were similar in midazolam- and propofol-treated patients, and ultimate treatment failure was less common with pentobarbital (3%) than with midazolam (21%) or propofol (20%) [49]. Different surgical options for refractory status epilepticus have been reported in the literature including focal resections, corpus callosotomy, hemispherectomy, and subpial transaction. Vagus nerve stimulation has also been reported to be useful in a few cases. Low-frequency stimulation through subdural electrodes has been used to suppress seizures in refractory status epilepticus.

Prognosis

The mortality of status epilepticus varies from 11% to 34% with rates higher in adults (15–49%) than in children (3–15%) [50]. The case fatality in the first month after status epilepticus was 21% and is primarily in those with acute symptomatic status epilepticus associated with illnesses that have a high mortality [51]. In the adult population, status epilepticus is often secondary to anoxia, hypoxia, stroke, metabolic abnormalities, brain tumor, or head injury, which has the highest mortality. In children, higher mortality is associated with severe acute encephalopathies and progressive encephalopathies. The lowest mortality rate is found in febrile and idiopathic status epilepticus.

Etiology, time from onset of status epilepticus to the administration of medical treatment, duration of seizures, age, and response to early treatment are some of the variables that predict the outcome of status epilepticus. Status epilepticus is also associated with increased morbidity in terms of recurrence of status epilepticus with some cases leading to the development of subsequent epilepsy and progression to intractable epilepsy. Other serious comorbidities include cognitive deficits, such as a decline in short-term memory and intelligence quotient (IQ) scores [52]. The risk of unprovoked seizures is 3×34 times higher after acute symptomatic status epilepticus (41%) than after single seizures (13%), and the risk of developing a febrile seizure is much higher after status epilepticus than after simple febrile convulsions [53].

Summary

Status epilepticus is a major medical and neurologic emergency. Incidence shows variations with ethnicity (highest among blacks), gender (male higher), and age (highest among children and elderly population). Etiology is different in adults and children. A notable point with regards to etiology is that an individual with no history of epilepsy can present with status epilepticus. Continuous, generalized convulsive seizures are considered to be status epilepticus when they last more than 5 min or there are two or more seizures during which the patient does not return to baseline consciousness. The evolution of status epilepticus in different phases has been well described. Early treatment of status epilepticus is required as time-dependent pharmacoresistance has been described in animal studies. Even with current best practice, 50% of patients with refractory GCSE will die. Therefore there is an urgent need for new treatment options that can stop seizures more effectively and safely than current drugs.

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Central Nervous System Infections

11

Karen L. Roos

Abstract

The central nervous system infections that are neurological emergencies are meningitis, encephalitis, focal infectious mass lesions (brain abscess and subdural empyema), and spinal epidural abscess. This chapter will review the diagnosis and management of these neuroinfectious diseases.

Keywords

Meningitis • Encephalitis • Subdural empyema • Spinal epidural abscess

Meningitis

Meningitis is the most worrisome illness in the patient who presents to the emergency department with fever and headache. The classic triad of meningitis is fever, headache and meningismus, which is resistance to passive flexion of the neck due to pain. A stiff neck is the pathognomonic sign of meningeal irritation from any process.

Viral Meningitis

The clinical presentation of viral meningitis is fever, headache, nausea, photophobia and meningismus. Individuals with viral meningitis appear acutely ill and complain of a severe headache but are typically awake and alert. They may be lethargic, but are not stuporous or comatose. They do not present with seizures or focal neurological deficits.

The most common viruses to cause meningitis are the enteroviruses. The enteroviruses are the coxsackievirues, the echoviruses, and the viruses identified by number (enteroviruses 68–71). Herpes simplex virus type 2 (HSV-2), the human immunodeficiency virus (HIV-1), and the arthropod-borne viruses are also fairly common etiologic agents of meningitis.

Bacterial Meningitis

Patients with bacterial meningitis have either a subacute illness that has progressed over 24–72 h or a fulminant illness that developed over several hours. The initial symptoms of bacterial meningitis include any of the following: fever, headache, lethargy, stupor, confusion, nausea, vomiting,

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and photophobia. It is the altered level of consciousness that is the single symptom that distinguishes the patient with bacterial meningitis from the patient with viral meningitis. Seizures occur in 40% of patients with bacterial meningitis and typically occur in the first week of illness. In children, symptoms of bacterial meningitis are often preceded by an upper respiratory tract infection or an otitis media [1]. Nuchal rigidity may be absent early in the course of the illness; therefore, the absence of a stiff neck should not exclude the diagnosis of bacterial meningitis [2]. In both children and adults, vomiting is a frequent, but often overlooked, symptom of bacterial meningitis.

Predisposing and associated conditions for bacterial meningitis are as follows: (1) pneumonia, (2) otitis, mastoiditis, sinusitis, (3) diabetes, (4) alcoholism, (5) head trauma with basilar skull fracture, (6) asplenia, (7) congenital or acquired deficiency in the terminal common complement pathway (C3 and C5 to C9) or hypo- or agammaglobulinemia, and (8) endocarditis. It is important to note that the predisposing and associated conditions are often not known at the time of presentation.

The most common causative organisms of bacterial meningitis are *Streptococcus pneumoniae* and *Neisseria meningitidis.* The incidence of meningitis due to *N. meningitidis* has decreased with the vaccination of children and adolescents with the tetravalent (serogroups A, C, W-135, and Y) meningococcal glycoconjugate vaccine. The vaccine does not contain serogroup B, which is responsible for one third of cases of meningococcal disease [3].

Meningitis due to otitis, mastoiditis, or sinusitis may be due to *Streptococci* spp. (including *S. pneumoniae*), gram-negative anaerobes, *S. aureus, Haemophilus* sp., or Enterobacteriaceae. Patients with congenital or acquired deficiency in the terminal common complement pathway (C3 and C5 to C9), immunoglobulin deficiency or asplenia are at risk for meningitis due to *N. meningitidis* or *S. pneumoniae.* Patients with defects of cell-mediated immunity are at risk for meningitis due to *Listeria monocytogenes.* Meningitis complicating endocarditis may be due to viridans streptococci, *S. aureus, S. bovis,* the HACEK group (*Haemophilus* sp., *Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, and Kingella kingae*), or enterococci. Meningitis in the postneurosurgical patient and/or the patient with a ventriculostomy may be due to staphylococci, gram-negative bacilli, or anaerobes.

The presence of a diffuse erythematous maculopapular and/or petechial rash on the trunk and lower extremities, in the mucous membranes and conjunctiva, and occasionally on the palms and soles is typical of meningococcemia. It is the location of the rash on the trunk and lower extremities that should raise a concern for meningococcemia. A viral exanthem typically appears as a maculopapular rash on the head and neck.

Aseptic Meningitis

Aseptic meningitis is an old term that is of little use today. The criteria for aseptic meningitis were described by Wallgren in 1925 and are as follows: (1) acute onset; (2) fever, headache, and meningismus; (3) CSF abnormalities typical of meningitis with a predominance of mononuclear cells; (4) absence of bacteria by smear and by culture of cerebrospinal fluid; (5) no parameningeal focus of infection; and (6) self-limited benign course [4–6]. The term aseptic meningitis can really only be applied to viral meningitis, meningitis following posterior fossa surgery, and medication-induced meningitis, and as such, should be labeled by these terms rather than as an "aseptic meningitis." In both medication-induced meningitis and meningitis following posterior fossa surgery, the CSF glucose concentration may be low.

Lyme Disease

Lyme disease, due to the spirochete *Borrelia burgdorferi*, is endemic in New England, parts of Minnesota and Wisconsin and the mid-Atlantic states, and in areas of northern California. Patients with meningitis due to *B. burgdorferi* complain

of headache and fatigue and some have myalgias and arthralgias. A unilateral or bilateral facial nerve palsy may be present or a painful radiculopathy. Inquire about and examine the patient for the classic erythema migrans lesion.

Tuberculous Meningitis

Suspect tuberculous meningitis in the patient with either several weeks of headache, fever, and night sweats or a fulminant presentation with fever, altered mental status, and focal neurological deficits.

Differential Diagnosis

The differential diagnosis of the triad of fever, headache, and stiff neck is bacterial or viral meningitis, fungal meningitis, tuberculous meningitis, syphilitic meningitis, drug-induced aseptic meningitis, carcinomatous or lymphomatous meningitis, and aseptic meningitis associated with inflammatory diseases (systemic lupus erythematosus, sarcoidosis, Sjögren's syndrome, etc.). If the presentation is that of headache and stiff neck, subarachnoid hemorrhage is in the differential diagnosis [7]. When impaired consciousness, focal neurological deficits, or new onset seizures are added to the classic triad, the differential diagnosis includes viral encephalitis, intracranial venous thrombosis, tick-borne bacterial infections, and infectious intracranial mass lesions. The differential diagnosis in HIV-infected patients who present with meningeal signs includes, in addition to meningitis caused by HIV, meningitis caused by *Cryptococcus neoformans*, *Mycobacterium tuberculosis*, and *Treponema pallidum*.

Initial Management

The patient with fever and headache should be managed as if they have bacterial meningitis until bacterial meningitis is ruled out. Recommendations for initial management include adjunctive and antimicrobial therapy and the diagnostic studies that have the highest yield for distinguishing between bacterial and viral meningitis. Those diagnostic studies include Gram's stain and bacterial blood cultures, serum procalcitonin and C-reactive protein, and spinal fluid analysis. Serum procalcitonin (>2 ng/mL) and C-reactive protein (>40 mg/L) are significantly higher in patients with bacterial meningitis than in those with viral meningitis, and can help in diagnosis when the results of spinal fluid analysis are available.

Empiric antimicrobial therapy for bacterial meningitis includes antibiotic therapy, as well as acyclovir for herpes simplex virus encephalitis as that is in the differential diagnosis and doxycycline for a tick-borne bacterial infection during the season when ticks are biting.

The most common causative organisms of community acquired bacterial meningitis in children and adults are *S. pneumoniae* and *N. meningitidis.* Empiric therapy of bacterial meningitis is based on predisposing and associated conditions (Table 11.1), and based on the possibility that a penicillin and cephalosporin-resistant strain of *S. pneumoniae* is the causative organism. In infants older than 1 month of age, children, and adults up to the age of 55, empiric therapy includes a third- or fourth-generation cephalosporin, either ceftriaxone (pediatric dose: 100 mg/kg/day in a 12-h dosing interval; adult dose: 2 g every 12 h) or cefepime (pediatric dose: 150 mg/kg/day in an 8-h dosing interval; adult dose: 2 g every 8 h) plus vancomycin (pediatric dose: 40–60 mg/kg/day in a 6- or 12-h dosing interval; adult dose: 45–60 mg/kg/day in an 8-h dosing interval). Metronidazole (1,500–2,000 mg/day in an 8-h dosing interval) is added to the empiric regimen to cover anaerobic bacteria in patients with the predisposing conditions of otitis, mastoiditis, sinusitis, neurosurgical procedures, and head trauma. Ampicillin should be added to the empiric regimen for coverage of *L. monocytogenes* in individuals over the age of 55 years, and in individuals with impaired cell-mediated immunity due to a chronic illness,

Table 11.1 Empiric antibiotic therapy based on predisposing and associated conditions

Predisposing condition	Bacterial pathogen	Antibiotic
Neonate	Group B streptococcus, *Escherichia coli*, *Listeria monocytogenes*	Ampicillin plus cefotaxime or an aminoglycoside
Children and adults—community acquired	*Streptococcus pneumoniae* and *Neisseria meningitidis*	Third- or fourth-generation cephalosporin plus vancomycin
Otitis, mastoiditis, sinusitis	Streptococci spp., gram-negative anaerobes (*Bacteroides* sp., *Fusobacterium* sp.), *S. aureus, Haemophilus* sp., Enterobacteriaceae	Third- or fourth-generation cephalosporin plus vancomycin plus metronidazole
Adults over the age of 55 and those with chronic illness	*S. pneumoniae,* gram-negative bacilli, *N. meningitidis, L. monocytogenes, Haemophilus influenzae*	Third- or fourth-generation cephalosporin plus vancomycin plus ampicillin
Endocarditis	Viridans streptococci, *S. aureus*, *Streptococcus bovis,* HACEK group, enterococci	Third- or fourth-generation cephalosporin plus vancomycin
Immunosuppressed	*S. pneumoniae, L. monocytogenes, H. influenzae*	Third- or fourth-generation cephalosporin plus vancomycin plus ampicillin
Postneurosurgical	Staphylococci, gram-negative bacilli	Vancomycin plus meropenem or vancomycin plus ceftazidime
Intraventricular device	Staphylococci, gram-negative bacilli, anaerobes	Vancomycin plus meropenem plus metronidazole or vancomycin plus ceftazidime plus metronidazole

organ transplantation, pregnancy, AIDS, malignancy, or immunosuppressive therapy, if they have not been on trimethoprim–sulfamethoxazole prophylactic therapy. Gentamicin is added to ampicillin in critically ill patients with *L. monocytogenes* meningitis. The dose of ampicillin is 2 g every 4 h, and the dose of gentamicin is 7.5 mg/kg/day in an 8-h dosing interval. Prior to or with the first dose of antibiotic, dexamethasone (infants and children 2 months of age and older: 0.15 mg/kg of body weight intravenously every 6 h for 2–4 days; adults: 10 mg intravenously every 6 h for 4 days) should be administered in patients with possible pneumococcal meningitis. Dexamethasone is administered either 15–20 min before the first dose of an antimicrobial agent or with the first dose of an antimicrobial agent.

In patients in whom herpes simplex virus encephalitis is suspected, acyclovir 10 mg/kg every 8 h is added to the empiric regimen. Doxycycline 100 mg every 12 h can be added to the empiric regimen during tick season if tick-borne bacterial infections are suspected. Doxycycline is relatively contraindicated in pregnant and lactating women and in children younger than 8 years of age.

Neuroimaging

A head CT scan prior to lumbar puncture is recommended in patients with any of the following criteria: an abnormal level of consciousness, a new onset seizure, a focal neurological deficit, an immunocompromised state, papilledema, or poorly visualized fundi. A CT scan prior to LP should also be obtained in patients from an endemic area for cysticercosis and at risk for an intraventricular cyst.

The primary argument against imaging prior to lumbar puncture is that imaging delays the lumbar puncture by 2–3 h and subsequently delays the initiation of antimicrobial therapy. Obtain blood cultures, initiate adjunctive and antimicrobial therapy, obtain a cranial CT if any of the above criteria are met, and then perform spinal fluid analysis.

Spinal Fluid Analysis

The CSF abnormalities characteristic of bacterial meningitis are:

- An opening pressure >180 mm H_2O.
- A polymorphonuclear pleocytosis. The CSF should be examined promptly after it is obtained because white blood cells in the CSF begin to lyse after about 90 min.
- A low glucose concentration. A glucose concentration of <40 mg/dL occurs in approximately 58% of patients with bacterial meningitis. A normal CSF-to-serum glucose ratio is 0.6. A CSF-to-serum glucose ratio of less than 0.31 is seen in approximately 70% of patients with bacterial meningitis.
- An elevated protein concentration.
- Gram's stain is positive in identifying the organism in 60–90% of cases of bacterial meningitis [8]. However, the probability of detecting bacteria on a Gram's stain specimen depends on the number of organisms present. Most smears will be positive when the CSF bacterial concentration is $>10^5$ CFU/mL. Only 25% of smears are positive when the bacterial concentration is 10^3 CFU/mL or less [1].
- Latex agglutination tests, which detect the antigens of common meningeal pathogens, are no longer routinely available or recommended for the rapid determination of the bacterial etiology of meningitis.
- Cerebrospinal fluid PCR assays have been developed to detect bacterial nucleic acid in CSF. There is a 16S ribosomal DNA-conserved sequence broad-based bacterial PCR that is routinely available, and a PCR for the detection of *N. meningitidis* and *S. pneumoniae* that is available in many hospitals. The CSF PCR assays for *Escherichia coli, Streptococcus agalactiae, Staphylococcus aureus, Haemophilus influenzae, L. monocytogenes*, and *Mycoplasma pneumoniae* are less readily available [9].
- The sensitivity and specificity of bacterial PCRs have not been defined. PCR will not replace culture as culture is critical for antimicrobial sensitivity testing.

Table 11.2 Cerebrospinal fluid studies for meningitis

Cell count with differential
Glucose and protein concentration
Stain and culture
• Gram's stain and bacterial culture
• India ink and fungal culture
• Viral culture
• Acid fast smear and *M. tuberculosis* culture
Antigens
• Cryptococcal polysaccharide antigen
• Histoplasma polysaccharide antigen
Polymerase chain reaction
• Broad-range bacterial PCR (16S ribosomal DNA)
• Specific meningeal pathogen PCR
• Reverse transcriptase PCR for enteroviruses
• PCR for herpes simplex virus type 1 and 2
• PCR for West Nile virus
• PCR for Epstein–Barr virus
• PCR for varicella zoster virus
• PCR for *M. tuberculosis*
• PCR for HIV RNA
Antibodies
• Herpes simplex virus (serum:CSF antibody ratio of <20:1)
• Varicella zoster virus IgM, and IgG antibody index
• Arthropod-borne viruses (West Nile virus IgM)
• *Borrelia burgdorferi* antibody index
• *C. immitis* complement fixation antibody
• VDRL, FTA-ABS

The CSF abnormalities typical of viral meningitis are:

- A normal opening pressure
- A lymphocytic pleocytosis
- A normal or mildly decreased glucose concentration
- A normal or mildly elevated protein concentration

Table 11.2 provides a list of cerebrospinal fluid diagnostic studies for the patient with suspected meningitis. The basic studies that should be performed on CSF in every patient with fever, headache, and meningismus are the following: (1) cell count with differential, (2) glucose and protein concentration, (3) Gram's stain and bacterial culture, (4) viral culture for enteroviruses, (5) the broad-based bacterial PCR (16S ribosomal DNA) if available, and (6) the reverse transcriptase PCR for enteroviruses. The remaining diagnostic tests listed in Table 11.2 should be obtained

Table 11.3 Appearance of the organism on Gram's stain

Organism	Gram's stain
Neisseria meningitidis	Biscuit- or kidney-shaped gram-negative diplococci
Streptococcus pneumoniae	Gram-positive lancet-shaped diplococci which tend to associate in pairs rather than in short chains
Escherichia coli	Gram-negative bacilli
Pseudomonas aeruginosa	Gram-negative bacilli
Listeria monocytogenes	Gram-positive rod[a]
Staphylococcus aureus	Gram-positive cocci
Staphylococcus epidermidis	Gram-positive cocci

[a]*Listeria monocytogenes* may appear coccoid on Gram's stains of clinical specimens, particularly CSF, and are often mistaken for pneumococci. *Listeria monocytogenes* resembles diphtheroids and may thus be dismissed as a contaminant.

depending on the time of the year (i.e., if mosquitoes are biting), place of residence and travel history (i.e., fungal antigens and antibodies, *B. burgdorferi* antibodies), and risk factors (i.e., HIV, herpes simplex virus-2, VDRL). Meningitis due to *M. tuberculosis* is a consideration in the patient with a fulminant presentation and in the patient with a subacute course of illness.

A Gram's stain on CSF can be completed within minutes. When positive, the physician is paged with the results. Table 11.3 lists the appearance of the organism on Gram's stain. Never send tube #1 for Gram's stain as the CSF in tube #1 is at risk for being contaminated by *Staphylococcus epidermidis* that is normally found on the skin. This will result in a false-positive result of gram-positive cocci in CSF.

There may initially be a predominance of polymorphonuclear leukocytes in enteroviral meningitis early in the disease course with a transition to a lymphocytic pleocytosis within 24 h. Enteroviruses can either be isolated in CSF culture or detected in CSF by the reverse transcriptase polymerase chain reaction (RT-PCR) technique or both. Serology should be sent to detect a fourfold increase in IgG between acute and convalescent sera obtained 4 weeks later. Herpes simplex virus type 2 DNA can be detected in CSF by PCR. CSF culture is positive for HSV-2 in the majority of cases of meningitis associated with primary genital herpes, but is rarely positive in cases of meningitis associated with recurrent episodes of genital herpes. HIV-1 RNA levels can be measured in CSF and the virus can be cultured from CSF.

In meningitis due to an arthropod-borne virus, there may be a polymorphonuclear leukocytosis early in infection with a shift to a lymphocytic or mononuclear pleocytosis during the first week of illness. Patients with West Nile virus meningitis may have a persistent CSF neutrophilic pleocytosis. There is a CSF PCR test available for West Nile virus, but the sensitivity and specificity has not been defined. The best diagnostic test for West Nile virus meningitis is the detection of West Nile virus IgM in CSF, but this may not be positive until 7 days after the onset of symptoms. The identification of an arthropod-borne virus as the causative agent of meningitis is often dependent on serology. According to The Centers for Disease Control and Prevention, a confirmed case of arboviral meningitis is defined as a febrile illness with mild neurological symptoms during a period when arboviral transmission is likely to occur plus at least one of the following criteria: (1) fourfold or greater increase in serum antibody titer between acute and convalescent sera; (2) viral isolation from tissue, blood, or CSF; or (3) specific immunoglobulin M (IgM) antibody to an arbovirus in the CSF.

The diagnosis of Lyme disease meningitis typically begins with a serum ELISA (enzyme linked immunosorbent assay) to measure antibody to *B. burgdorferi.* A positive result is confirmed with a Western blot. Examination of the CSF demonstrates a lymphocytic pleocytosis with a normal glucose concentration and a mild to moderately elevated protein concentration. Intrathecal anti-*Borrelia burgdorferi* antibodies can be detected. The demonstration of anti-*Borrelia burgdorferi* antibodies in CSF should not be regarded as definitive evidence of neurologic Lyme disease based on the assumption that the presence of antibodies in CSF is evidence of intrathecal antibody production. The determination of the intrathecal production of antibodies to an organism requires more than the detection of antibodies in CSF, as antibodies can be passively transferred from

Table 11.4 Recommendations for specific antibiotic therapy in bacterial meningitis

Microorganism	Antibiotic
Streptococcus pneumoniae	
Penicillin susceptible MIC <0.1 mg/L	Penicillin G or ceftriaxone (or cefotaxime or cefepime)
Penicillin tolerant (MIC 0.1–1.0 mg/L)	Ceftriaxone (or cefotaxime or cefepime or meropenem)
Penicillin resistant (MIC >1 mg/L) or cefotaxime or ceftriaxone MIC ≥1 mg/L	Cefepime (or cefotaxime or ceftriaxone) plus vancomycin
Neisseria meningitidis	Penicillin G or ampicillin Ceftriaxone or cefotaxime for penicillin-resistant strains
Listeria monocytogenes	Ampicillin Ampicillin plus gentamicin (see text)
Streptococcus agalactiae (group B streptococci)	Ampicillin or penicillin G or cefotaxime
Escherichia coli and other Enterobacteriaceae	Ceftriaxone or cefotaxime or cefepime
Pseudomonas aeruginosa	Meropenem or cefepime or ceftazidime
Staphylococcus aureus	
Methicillin susceptible	Nafcillin or oxacillin
Methicillin resistant	Vancomycin
Staphylococcus epidermidis	Vancomycin or linezolid
Haemophilus influenzae	Ceftriaxone or cefotaxime or cefepime
Gram-positive anaerobic bacteria—*Actinomyces, Propionibacterium* species Gram-negative anaerobic bacteria—*Fusobacterium, Bacteroides* species	Metronidazole

serum to CSF, and Lyme antibodies may persist in the CSF for years. An antibody index is recommended to detect the intrathecal production of antibodies. The antibody index is the ratio of (anti-Borrelia IgG in CSF/anti-Borrelia IgG in serum) to (total IgG in CSF/total IgG in serum) [10]. The antibody index is, in general, considered positive when the result is >1.3–1.5.

The CSF abnormalities characteristic of asymptomatic and symptomatic syphilitic meningitis are a mononuclear pleocytosis, a slightly elevated protein concentration, and a positive VDRL. A positive CSF FTA-ABS is not diagnostic of neurosyphilis, but a negative FTA-ABS is evidence against the diagnosis.

In tuberculous meningitis, the CSF glucose concentration is typically only mildly decreased (35–40 mg/dL).

Therapy of Bacterial Meningitis

Once the meningeal pathogen has been identified, antibiotic therapy is modified. Table 11.4 lists the recommended antibiotics based on bacterial pathogen and therapy should be further modified when the results of antimicrobial sensitivity testing is available. Table 11.5 is a list of the recommended dose.

The Infectious Diseases Society of America (IDSA) practice guidelines for the management of bacterial meningitis [11] and the European Federation of Neurological Societies (EFNS) guideline on the management of community-acquired bacterial meningitis [12] recommend the use of dexamethasone (0.15 mg/kg every 6 h for 2–4 days) in adults with suspected or proven pneumococcal meningitis. The first dose should be administered 10–20 min before, or at least concomitant with, the first dose of antimicrobial agent. The EFNS Task Force recommends, in addition to the above, that dexamethasone be administered to children with suspected pneumococcal or *H. influenzae* type b meningitis. The IDSA practice guidelines recommend adjunctive therapy with dexamethasone in infants and children with *H. influenzae* type b meningitis, but recognizes there is controversy concerning the use of adjunctive dexamethasone therapy in infants and children with pneumococcal meningitis. The recommendation is that the potential benefits be weighed against the potential risks.

Table 11.5 Recommended dose of antibiotic therapy

Antibiotic agent	Total daily dosage (dosing interval in hours)
Ampicillin	Neonate: 150 mg/kg/day (q8 h) Infants and children: 300 mg/kg/day (q6 h) Adult: 12 g/day (q4–6 h)
Cefepime	Infants and children: 150 mg/kg/day (q8 h) Adult: 6 g/day (q8 h)
Cefotaxime	Neonate: 100–150 mg/kg/day (q8–12 h) Infants and children: 225–300 mg/kg/day (q6–8 h) Adult: 8–12 g/day (q4–6 h)
Ceftriaxone	Infants and children: 80–100 mg/kg/day (q12 h) Adult: 4 g/day (q12 h)
Gentamicin	Neonate: 5 mg/kg/day (q12 h) Infants and children: 7.5 mg/kg/day (q8 h) Adult: 5 mg/kg/day (q8 h)
Meropenem	Infants and children: 120 mg/kg/day (q8 h) Adult: 6 g/day (q8 h)
Metronidazole	Infants and children: 30 mg/kg/day (q6 h) Adult dose: 1,500–2,000 mg/day (q6 h)
Nafcillin	Neonates: 75 mg/kg/day (q8–12 h) Infants and children: 200 mg/kg/day (q6 h) Adult: 9–12 g/day (q4 h)
Penicillin G	Neonates: 0.15–0.2 mU/kg/day (q8–12 h) Infants and children: 0.3 mU/kg/day (q4–6 h) Adult: 24 million units/day (q4–6 h)
Rifampin	Infants and children: 10–20 mg/kg/day (q12–24 h) Adults: 600–1,200 mg/day (q12 h)
Vancomycin	Neonates: 20–30 mg/kg/day (q8–12 h) Infants and children: 60 mg/kg/day (q6 h) Adults: 45–60 mg/kg/day (q6–12 h)[a]
Chemoprophylaxis *Neisseria meningitidis*	Rifampin 600 mg twice daily for 2 days or ceftriaxone 250 mg intramuscular

[a]Intraventricular vancomycin administration: children: 10 mg/day, adults: 20 mg/day.

The IDSA practice guidelines also acknowledge that "some authorities would initiate dexamethasone in all adults with suspected bacterial meningitis because the etiology of meningitis is not always ascertained at initial evaluation" [11].

Therapy of Viral Meningitis

Viral meningitis is treated with nonsteroidal anti-inflammatory agents and amitriptyline. The initial lumbar puncture is often therapeutic in relieving the headache for several hours, but the headache returns, and in the case of enteroviral meningitis, may be quite troublesome for weeks to come.

Therapy of Lyme Disease Meningitis

Lyme disease meningitis in adults and children ≥ 8 years of age is treated with doxycycline 200–400 mg/day in two divided doses for 10–14 days.

Therapy of Syphilitic Meningitis

Syphilitic meningitis is treated with intravenous aqueous crystalline penicillin G 3–4 mU every 4 h for 10–14 days.

Encephalitis

Encephalitis should be suspected in every patient with fever and headache and one or more of the following: an altered level of consciousness, behavioral abnormalities or confusion, new onset seizure activity, and focal neurological deficits. Fever is expected, but fever is never a constant clinical feature.

Encephalitis may be due to reactivation of a latent herpesvirus infection that was acquired in childhood (herpes simplex virus-1 and varicella zoster virus), primary infection with a herpesvirus, an arthropod-borne virus, a tick-borne bacterial infection, or rabies.

Epidemiologic clues that are helpful in establishing the etiologic agent of the encephalitis include the season of the year, occupational exposures and recreational activities, travel history, the immune status of the patient, recent or chronic illness and their treatment (i.e., the risk of PML with hematologic malignancies and

with immunomodulating agents), vaccination history, and prevalence of disease in the local community [13].

Herpes Simplex Virus-1

Herpes simplex virus-1 encephalitis presents with a subacute progression of fever, hemicranial headache, behavioral abnormalities, focal seizure activity, and focal neurologic deficits, most often dysphasia or hemiparesis. In addition to fever and headache, confusion and word finding difficulties are the most common signs.

Mosquito-Borne Viruses

Mosquito-borne viral infections may cause a mild febrile illness with headache, an aseptic meningitis, or an encephalitis. The onset of symptoms of encephalitis may be preceded by an influenza-like prodrome of fever, malaise, myalgias, and nausea and vomiting. These symptoms may be followed by confusion and seizures. Patients with West Nile virus encephalitis may have tremor, or a maculopapular or roseolar rash. Patients with West Nile virus encephalitis or St. Louis virus encephalitis may have an acute asymmetric flaccid weakness due to anterior horn cell disease (a poliomyelitis-like syndrome) or parkinsonian features.

Varicella Zoster Virus

Varicella zoster virus encephalitis occurs when previously acquired latent virus reactivates. Varicella zoster virus encephalitis due to the reactivation of latent varicella zoster virus can follow the cutaneous eruption of zoster, or occur in association with a diffuse varicella-like rash or occur without a varicella rash or a recent history of shingles. Approximately 40% of patients with varicella zoster virus encephalitis have no history of zoster or a varicella rash.

The characteristic clinical presentation of varicella zoster virus encephalitis is headache, malaise, confusion, and focal neurologic symptoms and signs. Varicella zoster virus encephalitis is due to ischemic and hemorrhagic infarctions of the cortical and subcortical gray matter and white matter. Multinucleated giant cells, inclusion bodies, herpesvirus particles, varicella zoster virus DNA, and antigen can be found in affected cerebral arteries. Vasculopathy may be recurrent and present with TIAs months after acute zoster [14]. Zoster reactivation may also cause demyelinating lesions or a ventriculitis and periventriculitis with hydrocephalus, altered mental status, and trouble with gait.

Tick-Borne Bacterial Infections

The most common tick-borne infection to cause encephalitis is *Rickettsia rickettsii* (Rocky Mountain spotted fever). Rocky Mountain spotted fever presents with fever, headache, altered mental status (stupor, confusion, delirium, and coma), seizures, and focal neurologic deficits. A petechial rash is characteristic of Rocky Mountain spotted fever. The rash of Rocky Mountain spotted fever consists initially of 1–5-mm pink macules that are often noted first on the wrists and ankles then spread centrally to the chest, face, and abdomen. The rash of Rocky Mountain spotted fever usually does not involve the mucous membranes. Petechial lesions in the axilla and around the ankles accompanied by lesions on the palms and soles of the feet are characteristic of Rocky Mountain spotted fever. The macules will initially blanch with pressure but after a few days they become fixed and turn dark red or purple. Diagnosis can be made by biopsy of the lesions.

Ehrlichia typically cause a mild illness, but two human ehrlichoses may cause fever, headache, and an altered mental status. The headache is often intense [15]. Ehrlichia are bacteria that infect mononuclear cells and polymorphonuclear leukocytes. Human monocytic ehrlichiosis is caused by *Ehrlichia chaffeensis,* and human granulocytic anaplasmosis is caused by *Anaplasma phagocytophilum.*

Table 11.6 Routine tests for encephalopathy

Metabolic	Infectious	Toxic
Electrolytes	CBC with differential	Serum and urine tox screens
Glucose	Blood cultures	
Creatinine	Chest X-ray	
Liver function tests	Urinalysis	
Ammonia	Urine culture	

Epstein–Barr Virus

Encephalitis can complicate acute Epstein–Barr virus infection, occur as a parainfectious immune-mediated demyelinating disorder, or present as an encephalomyeloradiculitis.

Rabies

Rabies due to the bite of a bat presents with focal neurological deficits (hemiparesis or hemisensory deficits), choreiform movements, myoclonus, seizures, and hallucinations. Phobic spasms are not a cardinal feature of bat rabies.

Differential Diagnosis

An encephalopathy is in the differential diagnosis of every patient with an altered level of consciousness or acute confusional state. An encephalopathy may be infectious, autoimmune, metabolic, toxic, ischemic, or anoxic. Although the specific diagnostic tests for encephalitis are serology, magnetic resonance imaging, specifically fluid attenuated inversion recovery (FLAIR) and diffusion-weighted imaging (DWI), and spinal fluid analysis, routine tests for encephalopathy should be sent as outlined in Table 11.6.

Initial Management

Initial management should be Gram's stain of blood, blood cultures, and PCR for bacterial nucleic acid where available. This is followed by empiric therapy for bacterial and viral encephalitis, and a tick-borne infection and includes dexamethasone, a third- or fourth-generation cephalosporin, vancomycin, ampicillin (for patients meeting the criteria described above), acyclovir, and doxycycline.

Table 11.7 Serological tests for encephalitis

IgM and IgG antibodies for
• St. Louis encephalitis virus
• West Nile encephalitis virus[a]
• Eastern equine encephalitis virus
• Western equine encephalitis virus
• Japanese encephalitis virus
• Dengue virus
• Epstein–Barr virus (VCA IgM and IgG and EBNA)
• Varicella zoster virus
• Herpes simplex virus-1
• Rabies virus
• HIV
Tick-borne bacterial infection
• IgG and IgM by indirect immunofluorescence for Rocky Mountain spotted fever[b]
• *Ehrlichia chaffeensis, Anaplasma phagocytophilum*

[a]West Nile virus IgM and IgG antibody titers that are positive by ELISA should be confirmed by the more specific plaque-reduction neutralization assay and cell culture.
[b]In addition to the indirect fluorescent antibody test for rickettsial infections, there are increasing enzyme-linked immunosorbent assays and flow immunoassays available, as well as PCR.

Diagnosis

Serology

Table 11.7 is a list of serological tests for encephalitis. The determination of which tests to send should be individualized for each patient based on the season of the year, the area where the patient lives or has traveled to, the patient's occupation and recreational activities, and the patient's risk factors.

During mosquito season, serological testing should be done to detect IgM and IgG antibodies to St. Louis encephalitis virus, West Nile encephalitis virus, and any other mosquito-borne viruses that are endemic in the area in which the patient has lived or traveled to. West Nile virus IgM and IgG antibody titers that are positive by enzyme-linked immunosorbent assay should be confirmed by the more specific plaque-reduction neutralization assay and cell culture. Serology should also

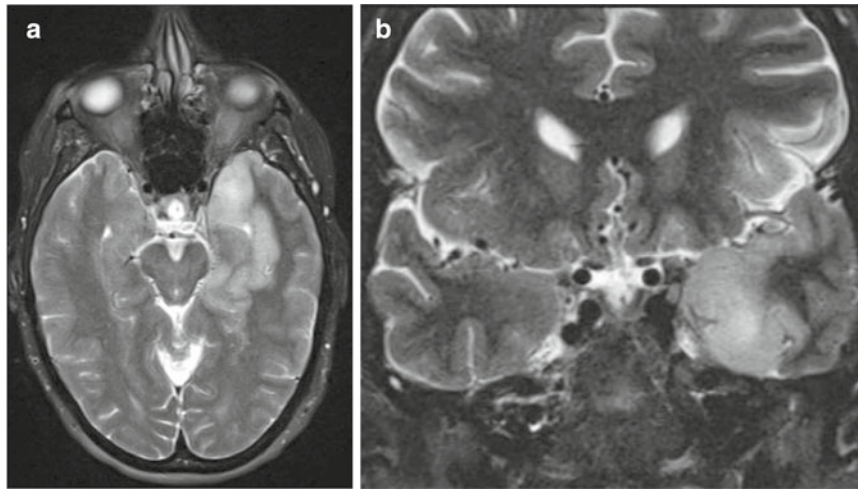

Fig. 11.1 (**a**) Axial and (**b**) coronal T2-weighted MRI demonstrating a lesion of increased signal intensity in the left anteromedial temporal lobe in HSV-1 encephalitis. Courtesy of Darren O'Neill M.D

be sent for rabies virus IgM and IgG if there is any possibility of exposure to a bat.

During the season when ticks are biting, serological testing to detect IgG and IgM by indirect fluorescent antibodies (IFA) and PCR assays for Rocky Mountain spotted fever should be obtained. Serial samples over a number of days are recommended to detect a rise in the antibody titer. The serological tests for rickettsial infections have a low sensitivity early in the disease [16]. Not all patients will have a serological response. Skin lesions should be biopsied. The diagnosis of infection with either *E. chaffeensis* or *A. phagocytophilum* is made by serology and by the examination of blood smears for morulae, which are Ehrlichia inclusion bodies, in mononuclear cells (*E. chaffeensis*) or polymorphonuclear leukocytes (*A. phagocytophilum*).

Use serology to diagnose acute Epstein–Barr virus infection. Acute Epstein–Barr virus infection is confirmed by the detection of antiviral capsid antigen (VCA) IgM antibodies and the absence of antibodies to virus-associated nuclear antigen (anti-EBNA IgG). Virus capsid antigen IgG antibodies develop after IgM antibodies. In subsequent serum samples (collected 36 days after the onset of illness), there should be a decrease in the VCA IgG antibody titer and an increase in anti-EBNA IgG. The detection of IgG antibodies against viral capsid antigen but no EBNA antibodies is also evidence of recent infection.

Neuroimaging

Herpes Simplex Virus-1

MR fluid attenuated inversion recovery (FLAIR), T2-weighted images, and diffusion-weighted sequences demonstrate an abnormal lesion of increased signal intensity in the temporal lobe in 90% of adult patients with herpes simplex virus encephalitis at 48 h from symptom onset (Fig. 11.1a, b).

Mosquito-Borne Virus

In encephalitis due to the flaviviruses (Japanese encephalitis virus, West Nile virus, and St. Louis encephalitis virus), hyperintense lesions on T2-weighted and FLAIR images may be seen in the thalami, substantia nigra, and basal ganglia.

Varicella Zoster Virus

On neuroimaging in varicella zoster virus encephalitis there may be evidence of ischemic and hemorrhagic infarctions of the cortical and subcortical gray matter and white matter, demyelinating lesions, or periventricular enhancement.

JC Virus

In progressive multifocal leukoencephalopathy, there are one or more nonenhancing subcortical white matter hyperintensities on T2 and FLAIR sequences.

Spinal Fluid Analysis

The characteristic findings on lumbar puncture in viral encephalitis are an increased opening pressure, a lymphocytic pleocytosis, a mild to moderate increase in the protein concentration, and a normal (or rarely mildly decreased) glucose concentration.

Herpes Simplex Virus-1

The CSF HSV-1 polymerase chain reaction (PCR) may be falsely negative in the first 72 h of symptoms of HSV encephalitis and detection rates decrease 10 days after the onset of symptoms. Antibodies to HSV-1 can be detected in CSF beginning at about day 8 after the onset of symptoms and for approximately 3 months. A serum:CSF antibody ratio of less than 20:1 is diagnostic of recent HSV-1 encephalitis.

Mosquito-Borne Viruses

Patients with West Nile virus encephalitis may have a CSF lymphocytic or neutrophilic pleocytosis. The best test for West Nile virus encephalitis or myelitis is the CSF IgM antibody test. This may take a week or longer to be positive. Serum West Nile virus IgM and IgG are evidence of exposure to the virus but cannot be used to make a diagnosis of West Nile virus encephalitis. The CSF PCR for West Nile virus nucleic acid has a poor sensitivity but a 100% specificity.

Tick-Borne Bacterial Infections

In Rocky Mountain spotted fever, human monocytic ehrlichiosis, and human granulocytic anaplasmosis, there is a CSF lymphocytic pleocytosis, but it is often low grade.

Varicella Zoster Virus

The best test for varicella zoster virus encephalitis is the detection of varicella zoster virus IgM antibodies in CSF.

Table 11.8 Cerebrospinal fluid diagnostic studies for encephalitis

Cell count with differential
Glucose and protein concentration
Stain and culture • Gram's stain and bacterial culture • India ink and fungal culture • Viral culture • Acid fast smear and *M. tuberculosis* culture
Antigens • Cryptococcal polysaccharide antigen • Histoplasma polysaccharide antigen
Polymerase chain reaction • Broad-range bacterial PCR (16S ribosomal DNA) • Specific meningeal pathogen PCR • Reverse transcriptase PCR for enteroviruses • PCR for herpes simplex virus type 1 and 2 • PCR for West Nile virus • PCR for Epstein–Barr virus • PCR for varicella zoster virus • PCR for JC virus • PCR for *M. tuberculosis* • PCR for HIV RNA • RT-PCR for rabies virus
Antibodies • Herpes simplex virus (serum:CSF antibody ratio of <20:1) • Varicella zoster virus • Arthropod-borne viruses • *C. immitis* complement fixation antibody • Rabies virus

Pitfalls

Epstein–Barr virus DNA can be found in peripheral blood latently infected mononuclear cells and may be positive in CSF in any CNS inflammatory disorder.

The detection of HHV-6 nucleic acid in CSF is not definitive evidence that HHV-6 is the etiological organism of the encephalitis. Send CSF for HHV-6 IgM.

Pearl

A rhombencephalitis (brainstem encephalitis), presenting with cranial nerve deficits and ataxia, may be due to HSV-1, enterovirus 71, or *L. monocytogenes*.

Table 11.8 is a list of the cerebrospinal fluid diagnostic studies for encephalitis.

Therapy

Herpes simplex virus-1 encephalitis is treated with acyclovir 10 mg/kg every 8 h for 21 days.

Varicella zoster virus encephalitis is treated with acyclovir 10–15 mg/kg every 8 h for a minimum of 14 days.

The tick-borne bacterial infections are treated with doxycycline 100 mg every 12 h for a minimum of 7 days and for at least 48 h after defervescence.

A number of agents have been investigated for the treatment of mosquito-borne viral encephalitis, many of which have been specifically investigated for West Nile virus encephalitis. These agents include ribavirin, interferon, and intravenous immunoglobulin containing high titers of anti-West Nile virus antibodies. None of these agents has been shown to be efficacious to date, but trials are ongoing.

Parainfectious or Postinfectious Encephalitis

Parainfectious or postinfectious immune-mediated encephalitis occurs within days to weeks of a viral infection, such as H1N1, or a vaccination [17]. This is an acute monophasic, inflammatory disorder of the central nervous system. It is primarily a disease of white matter, but gray matter may also be affected. There is typically an abrupt onset of multifocal neurological deficits and an altered level of consciousness days to weeks after a viral illness or vaccination. On T2-weighted and FLAIR magnetic resonance imaging, there are bilateral, asymmetric areas of increased signal abnormality in the subcortical white matter, cerebellum, periventricular white matter, and brainstem. On T1 imaging, the lesions enhance in a nodular, spotty, ring, or heterogenous pattern after the administration of gadolinium. Spinal fluid analysis demonstrates a lymphocytic or mononuclear pleocytosis, a normal glucose concentration, and an elevated protein concentration. Myelin basic protein and oligoclonal bands may be detected. Therapy is with intravenous high-dose corticosteroids. Plasma exchange is recommended for patients who do not respond to treatment with corticosteroids.

Infectious Mass Lesions

A brain abscess or a subdural empyema may present with fever, headache, focal neurological deficits, and an altered level of consciousness. The causative organism of an infectious mass lesion can be predicted from the suspected source of infection (i.e., sinusitis, otitis media, dental infections, trauma, and neurosurgical procedures), but in general, empiric antimicrobial therapy is initiated with a combination of a third- or fourth-generation cephalosporin, vancomycin, and metronidazole (see Table 11.5). Neuroimaging demonstrates the lesion. A subdural empyema requires emergent neurosurgical evacuation as the evolution of an empyema tends to be remarkably rapid once infection is established in the subdural space. As the empyema enlarges, there is a significant risk of increased intracranial pressure from the expanding mass lesion and brain herniation. Identification of the causative organism or organisms of a brain abscess is made by stereotactic aspiration, Gram's stain and culture of the purulent contents of the lesion, and of a subdural empyema, by Gram's stain and culture of the pus at the time of surgical evacuation of the empyema. Once the organism has been identified and the results of antimicrobial sensitivity testing are known, antimicrobial therapy is modified accordingly (see Table 11.5).

Spinal Epidural Abscess

A spinal epidural abscess is a purulent infection in the space outside the dura but within the spinal canal. An epidural abscess may develop from hematogenous spread of infection from a remote site of infection, by direct extension from a contiguous infection, such as a skin or soft tissue infection, or by inoculation of microorganisms into the epidural space during an invasive spinal

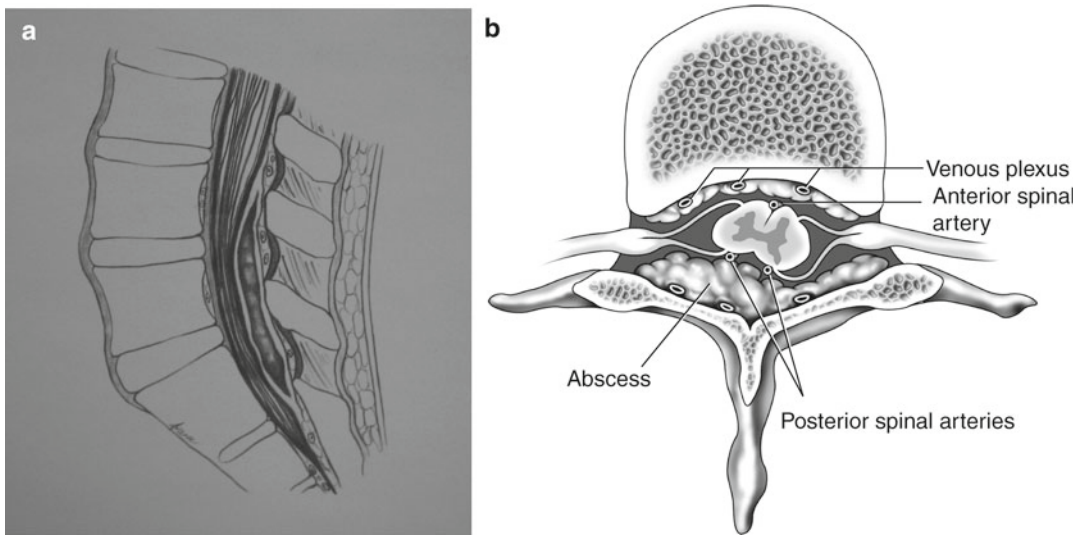

Fig. 11.2 (**a**) Sagittal and (**b**) axial images of spinal epidural abscess in the dorsal epidural space. From Roos KL, ed. Principles of Neurologic Infectious Diseases. New York: McGraw-Hill, 2005, p. 346. Reproduced with permission of the McGraw-Hill Companies

procedure. Risk factors for spinal epidural abscess include diabetes mellitus, intravenous drug abuse, trauma, an immunocompromised state, and invasive procedures (injections in the epidural space, spinal catheters, and spinal operations) [18]. An epidural abscess is more common in the posterior epidural space of the spinal canal, but those associated with osteomyelitis/discitis have been reported to be more common in the anterior epidural space [19].

The clinical presentation of a spinal epidural abscess was described by Heusner in 1948 [20]. The initial symptom is back pain at the spinal level of the epidural abscess. About 50% of patients have fever. Back pain is followed by radicular pain due to nerve root compression. This is followed by the development of a neurological deficit with paresis of appendicular musculature, loss of sensation below the level of the lesion, and loss of bowel and bladder control. Finally, there is paraplegia and loss of all sensory modalities below the level of the lesion.

The most common causative organisms of a spinal epidural abscess are *S. aureus,* coagulase-negative staphylococci, and gram-negative bacilli [21]. Spinal cord injury is due to either direct mechanical compression from the abscess or a result of ischemia from septic thrombophlebitis or a combination of these. A spinal epidural abscess may develop in the dorsal (Fig. 11.2a, b) or ventral epidural space (Fig. 11.3) [21].

Magnetic resonance imaging with gadolinium is the procedure of choice to demonstrate a spinal epidural abscess. The erythrocyte sedimentation rate and C-reactive protein are almost always elevated and there is often evidence of a peripheral leukocytosis.

Empiric antibiotic therapy is initiated with vancomycin and a third- or fourth-generation cephalosporin. Emergency laminectomy with evacuation of the purulent material allows for decompression of the spinal cord and identification of the organism. Antimicrobial therapy is modified when the organism has been identified and the results of antimicrobial sensitivity testing are known. The preoperative neurological examination is the most important predictor of outcome. Emergency decompressive surgery is not

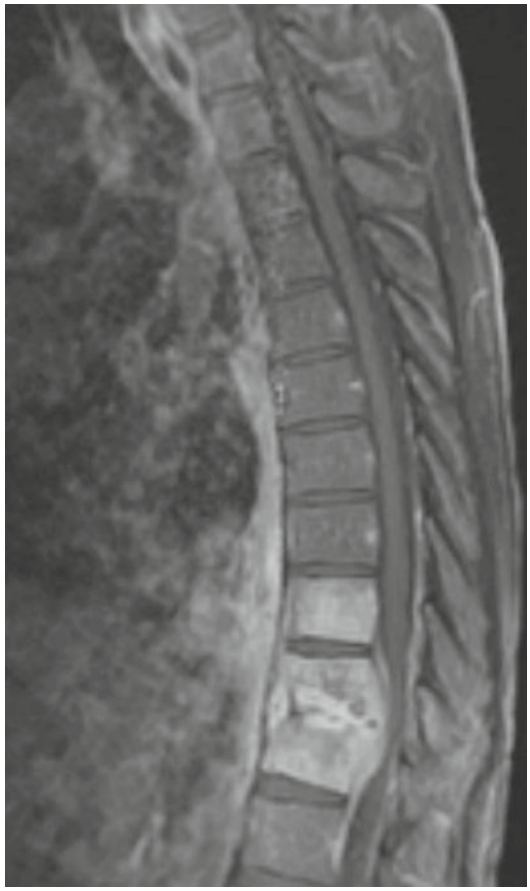

Fig. 11.3 Sagittal T1 postcontrast MRI demonstrating extensive abnormal enhancement within the bone marrow intervertebral disk space and ventral epidural space at the T10–11 level, compatible with discitis/osteomyelitis and associated ventral epidural abscess. Marked resultant mass effect and compression of the distal thoracic spinal cord. Abnormal enhancement also present within the T9 vertebral body. Courtesy of Darren O'Neill M.D

indicated in patients who have been paralyzed for greater than 24–36 h as the paralysis is unlikely to be reversible [22].

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Weakness (Guillain–Barré Syndrome)

12

Mengjing Huan and A. Gordon Smith

Abstract

Acute weakness is a common neurological emergency. One of the most frequent neuromuscular causes of acute weakness is Guillain–Barré syndrome (GBS). This chapter reviews the epidemiology, pathogenesis, differential diagnosis, clinical presentation, and variants of GBS. Treatment options are discussed including an evidence-based review of various immunomodulatory therapies and practical, symptomatic management. Finally, the chapter covers prognosis and differentiation between acute inflammatory demyelinating polyradiculoneuropathy (AIDP) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). This chapter aims to improve understanding and therefore diagnosis and management of a classic neuromuscular disease.

Keywords

Acute weakness • Demyelinating neuropathy • Guillain–Barré syndrome • Peripheral neuropathy

Acute weakness is a common neurological complaint with a myriad of causes. As with any neurological evaluation, localization of the disease process in the neuroaxis is the first step to establishing the diagnosis. This chapter will focus on peripheral nervous system causes of acute weakness, with a specific emphasis on Guillain–Barré syndrome. Guillain–Barré syndrome is the most common cause of acute flaccid weakness, with an annual incidence of 1.2–2.3 per 100,000 [1–3]. Advances in diagnosis and treatment of this condition have reduced the mortality rate of patients with Guillain–Barré syndrome. Clinicians should be able to promptly assess and treat patients presenting with Guillain–Barré syndrome, as well as recognize other disease processes that may present similarly.

In 1859, Octave Landry described ten cases of "ascending paralysis" both with and without sensory symptoms. Unfortunately, the initial pathological study did not examine peripheral nerves.

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Five years later, Louis Dumenil provided the first description of peripheral nerve pathology seen in "Landry's ascending paralysis" [4]. The cases reported by Landry were similar to what was eventually termed Guillain–Barré syndrome [5]. In 1916, French neurologists Georges Guillain, Jean-Alexandre Barré, and Andre Strohl presented a case of two soldiers with acute flaccid paralysis and areflexia with spontaneous recovery [6]. CSF protein concentration was elevated in these soldiers, while the cell count was normal. This formed the classic clinical description of Guillain–Barré syndrome with acute ascending symmetrical weakness, with decreased or absent tendon reflexes, and a CSF albuminocytological dissociation.

Epidemiology

Since the eradication of poliomyelitis in industrialized countries, Guillain–Barré syndrome has been recognized as the most common cause of acute weakness. The incidence increases with age and older patients tend to have a slower and more incomplete recovery. Guillain–Barré syndrome also occurs in infants and children. There is a 1.5:1 male to female ratio [2].

Guillain–Barré syndrome has a worldwide distribution, although regional differences exist. In North America and Europe, Guillain–Barré syndrome most commonly presents with the pattern of acute inflammatory demyelinating polyradiculoneuropathy (AIDP), accounting for up to 90–95% of cases. Axonal and cranial nerve variants account for 5–10% of US cases. In Japan, China, Central and South America, axonal variants may account for one-third to 50% of the cases [2]. This is likely a reflection of differences in immunogenic exposure, which sheds light on the pathogenesis of this disorder. Differences in genetic predisposition may also exist. There are temporary increases in regional incidence, which are also due to an increase in exposure to particular immunogens. One example is the increased incidence of the axonal variant of Guillain–Barré syndrome in northern China during the summer months of 1991–1992, which was eventually linked to an increase in *Campylobacter jejuni* infections. Electrophysiological and autopsy studies in this study demonstrated severe axonal damage in the motor nerves with relative sparing of sensory fibers [7]. Observations in these cases helped to establish the axonal motor variant of Guillain–Barré syndrome, acute motor axonal neuropathy.

Various infections have been associated with Guillain–Barré syndrome. About two thirds of patients report an antecedent infection within 1 month of onset of weakness [8]. Out of those with reported precedent infections, upper respiratory symptoms are most common (38–50%), followed by gastrointestinal symptoms (17–27%) [8, 9]. *C. jejuni* is the most frequently defined antecedent infection. Others include CMV, EBV, *Mycoplasma pneumoniae*, and *Haemophilus influenzae* [10–12].

The potential relationship between vaccines and Guillain–Barré syndrome has been controversial. Older formulations of the rabies vaccination derived from either the suckling mouse brain or mature sheep brain have been reported to induce Guillain–Barré symptom-like syndromes that are sometimes associated with an encephalomyelitis [13–15]. There has not been an association with the current chicken embryo derived rabies vaccine with Guillain–Barré syndrome [16]. Another well-studied association is the increase in the incidence of Guillain–Barré syndrome after the administration of the swine influenza vaccinations in 1976 [17]. Approximately 45 million Americans were immunized against an H1N1 influenza virus in 10 weeks. An apparent increase in the risk for Guillain–Barré syndrome was reported among those vaccinated. In the original retrospective study, the rate of Guillain–Barré syndrome within 6 weeks of vaccination was 8.8 cases per million. The calculated background incidence of Guillain–Barré syndrome was 0.7–4.6 cases per million persons in a 6-week period. Subsequent studies reanalyzed the data and found a persistent increased incidence of Guillain–Barré syndrome after vaccination [18]. This suggests a causal relationship between the swine flu vaccination and Guillain–Barré syndrome, although the exact nature of the relationship remains unknown. As of yet, there are no data suggesting an increased risk with

modern H1N1 vaccine. Other influenza vaccines following the 1976 program have not demonstrated a definitive causal relationship to the development of Guillain–Barré syndrome. Several authors have reported an increased incidence or case reports of Guillain–Barré syndrome following influenza, hepatitis, and tetanus vaccines [19–21]. Other studies have not found an excess of Guillain–Barré syndrome cases following vaccinations [22–24]. There are also reported cases of Guillain–Barré syndrome following quadrivalent conjugated meningococcal vaccine, but a clear causal relationship is not yet established [22]. The implications for patients who have a history of Guillain–Barré syndrome are not entirely clear. A Cochrane review of supportive and adjunctive treatment in Guillain–Barré syndrome suggests that immunizations should not be given in the acute phase of Guillain–Barré syndrome and possibly 1 year after symptoms, although the risk of recurrent Guillain–Barré syndrome following vaccination is overall very small [25]. However, risk and benefit analysis should be done for each patient with a history of Guillain–Barré syndrome.

Pathophysiology and Pathogenesis

Immune dysfunction as the basis of the pathogenesis of Guillain–Barré syndrome is suggested by the epidemiological association with antecedent infections and possibly vaccinations. This is further supported by pathological studies, associated antiglycolipid antibodies, and the beneficial effect of immunomodulatory therapies. Discussion of the pathophysiology of Guillain–Barré syndrome benefits from an appreciation of the different subtypes: classic AIDP pattern, axonal pattern, and cranial nerve pattern, which are described in greater detail in the following section under "Clinical Variants."

Pathological Studies

Pathological studies of AIDP have identified multifocal mononuclear infiltrates in peripheral nerves and roots [26]. Macrophages attack Schwann cells or intact myelin sheaths, producing demyelination. Axonal loss may also occur in those with severe disease [27].

In the axonal motor variant of Guillain–Barré syndrome, acute motor axonal neuropathy (AMAN), macrophages attack the nodes of Ranvier and insert between the axon and Schwann cell axolemma, producing conduction block along the axon. The northern Chinese variant of AMAN has not only a rapid decline but also a rapid recovery, which suggests that axonal conduction is interrupted, but true axonal degeneration is minor or predominantly distal [28, 29]. This may also be related to faster axonal repair in the young, as most northern Chinese cases involve children and young adults. However, most patients with axonal Guillain–Barré syndrome experience more rapid progression and greater peak and residual disability, reflecting primary axonal damage with Wallerian degeneration. Patients with motor and sensory involvement, acute motor sensory axonal neuropathy (AMSAN), also have a slow recovery. The pattern of macrophage attack is similar to that in AMAN, except dorsal roots are also involved. It is proposed that AMSAN may represent a more severe immunological attack on the axons, producing true axonal degeneration resulting in much slower repair despite cessation of the initial immune attack. There is little lymphocytic infiltration of the nerves or roots in either of the axonal variants. Autopsy studies have found antibodies and complement activation may be the primary dysimmune mechanism in axonal forms, with clustering at the nodes or Ranvier that may interrupt sodium channels [30].

Antiganglioside Antibodies

Antiganglioside antibodies are found in many variants of Guillain–Barré syndrome except the AIDP pattern (Table 12.1). Gangliosides are glycosphingolipids with extracellular carbohydrate residues with one (e.g., GM1 for "mono") or more (GD1 for "duo," GT1 for "tri," etc.) sialic acid molecules (Fig. 12.1). They are found in many tissues but are particularly abundant in neural tissues. Some studies report Guillain–Barré

Table 12.1 Guillain–Barré syndrome variants and associated antiganglioside antibodies

Guillain–Barré syndrome variants	Antibodies
AIDP	Unknown
AMAN	GM1, GM1b, GD1a, GalNac-GD1a
AMSAN	GM1, GM1b, GD1a
Miller Fisher	GQ1b, GT1a
Pharyngeal–cervical–brachial	GT1a
Overlap syndrome AIPD and Miller Fisher	GQ1b, GM1, GM1b, GD1a, GalNac-GD1a

Many antiganglioside antibodies have been discovered to be associated with specific variants of Guillain–Barré syndrome. The association with a specific pattern may be due to prevalence of these gangliosides in different regions of the nervous system. There are also antibodies against ganglioside complexes (i.e., more than one ganglioside) associated with different variants which need further characterization.
Adapted from Hughes [2].

syndrome-like syndromes induced by immunization against gangliosides in both animal and human models. For example, injection of bovine gangliosides had been popular for a period of time for treatment of conditions such as pain, sciatica, and stroke, and AMAN symptoms were seen in a small proportion of these patients. They also had antibodies to GM1 [31]. The mechanism is more complicated, however, as other studies of immunization against highly purified GM1 have produced high antibody titers without clinical evidence of disease. It is proposed that a protein, other than GM1, may be needed in conjunction to produce clinical symptoms, as the direct injections of antiganglioside antibodies do not induce disease [32].

The majority of AMAN patients have GM1 antibodies. The association is even stronger

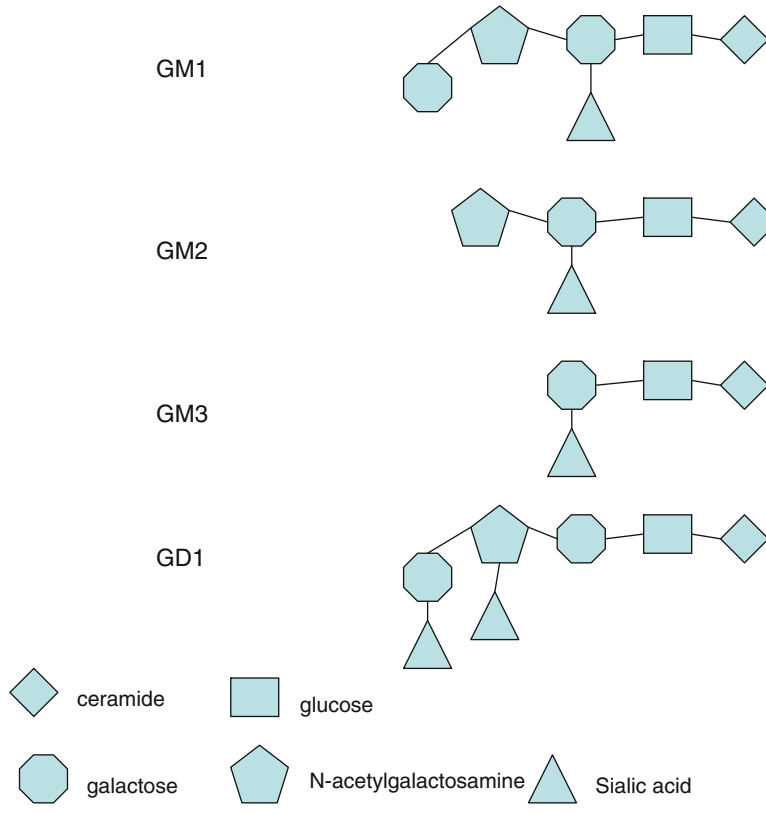

Fig. 12.1 Schematic drawing of gangliosides. "M" in GM1 or 2 or 3 represents only one sialic acid group (NANA). The number directly following G (for ganglioside) presents with combination of glucose, *N*-acetylgalactosamine and galactose attached to the ceramide component. For example, GD1 would be similar to GM1 except with an additional sialic acid (NANA) group on the molecule

in Miller Fisher variant, with GQ1b antibodies present in over 90% of the cases [33]. There is some localization correlation between the antibodies and clinical features. For example, GM1 is more prevalent in the ventral roots than in the dorsal roots, and syndromes with GM1 antibodies are associated with more motor symptoms. Likewise, GQ1b is more prevalent in oculomotor nerves than in spinal roots leading to cranial nerve predominant symptoms [34]. However, as seen in Table 12.1, antibodies may be associated with more than one clinical variant. They may be present in other diseases with a significant component of immune-mediated neuropathy, such as GM1 antibodies seen in multifocal motor neuropathy.

In addition to antibodies against one ganglioside, antibodies to ganglioside complexes have been identified in some cases of Guillain–Barré syndrome. For example, antibodies against GD1a/GD1b and/or GD1b/GT1b complexes have been found in patients with severe diseases requiring mechanical ventilation. In these patients, antibodies to individual gangliosides (e.g., GD1a) are absent or occur in much reduced quantities. In some cases of Miller Fisher syndrome without GQ1b antibodies, there may be antibodies against GQ1b/GM1 complexes instead [35, 36]. Antibodies to ganglioside complexes may activate complement system similar to individual gangliosides and cause injury to myelin or axons [35]. The exact significance of these antibodies awaits further characterization.

Antiganglioside antibodies cause nerve injury via complement activation. These antibodies bind to gangliosides or complexes on the nerve membrane resulting in complement fixation and membrane attack complex (MAC) formation. Calcium influx through MAC pores further elicit downstream events leading to nerve dysfunction and injury [37]. This mechanism suggests therapeutic possibilities with agents that can block complement activation or MAC formation.

Molecular Mimicry

C. jejuni infection may precede any variant of Guillain–Barré syndrome, but AMAN is the most common clinical syndrome. The strain of *C. jejuni* may predict the type of clinical manifestation, along with associated antiganglioside antibodies. *C. jejuni* strains producing AMAN symptoms have sialic acid structures in the bacterial cell walls mimicking GM1 that produce anti-GM1 antibodies when injected into a rabbit [38, 39]. Strains of *C. jejuni* inducing Miller Fisher variants often carry GQ1b-, GT1a-, or GD3-like epitopes and can induce similar pathological reactions when injected into animal models. Other organisms may also induce Guillain–Barré syndrome symptoms by molecular mimicry. *H. influenza* has GQ1b- or GM1-like bacterial cell wall components and *M. pneumoniae* may induce antibodies to galactocerebroside [33, 40, 41]. Thus, it is proposed that these antibodies produced by antecedent infections may cross-react with gangliosides in the patient's nervous system and form the basis of molecular mimicry in the pathogenesis of Guillain–Barré syndrome. However, not all cases of Guillain–Barré syndrome have known antecedent infections, and therefore, some other mechanism of induction of these antibodies must be present. Also, these infections can precede the AIDP variant, but antiganglioside antibodies have not been identified. Therefore, molecular mimicry, along with antiganglioside antibodies, provides a limited explanation of the pathogenesis of Guillain–Barré syndrome and not the complete picture.

Clinical Features

The classic features of Guillain–Barré syndrome are progressive weakness and areflexia over a course of days to weeks. By definition, the time to maximal weakness in Guillain–Barré syndrome is less than 4 weeks, differentiating it from chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), which has a progressive or relapsing course over at least 8 weeks. This definition leaves a spectrum of "subacute" inflammatory demyelinating polyradiculoneuropathy ("SIDP") with a time course between 4 and 8 weeks [42]. Whether this represents a distinct entity or exists at the extreme of AIDP or CIDP is

controversial. In general, 50% of patients with Guillain–Barré syndrome will reach maximal weakness by 2 weeks, and 90% by 4 weeks [43]. Guillain–Barré syndrome patients usually have spontaneous improvement, although this improvement may occur slowly over weeks to months.

Many patients report the initial onset of sensory symptoms (paresthesias) before motor symptoms. However, frank sensory loss as a chief complaint is not common, especially with minimal or no weakness. Weakness is the predominant symptom that brings patients to medical attention and most have symmetrical involvement. Although many classic cases were described as ascending weakness, a true stocking-glove pattern is unusual, as there is often concurrent inflammation of nerve roots resulting in proximal symptoms. Bilateral facial weakness is also common and may be more symptomatic on presentation than leg weakness. Bulbar weakness may also occur in severe cases. Respiratory weakness is the most worrisome symptom. Mechanical ventilation was required in 9.1% of all patients admitted for Guillain–Barré syndrome in one study [3]. Therapeutic trials treating patients who are unable to walk report intubation in up to one third of severely affected patients [21].

Areflexia or hyporeflexia is a cardinal feature of Guillain–Barré syndrome. Most patients have absent reflexes in the involved limbs, although in the early stages or in rare cases, only a reduction in reflexes may be seen. Areflexia helps to differentiate peripheral nerve involvement from CNS disease, with the exception of weakness from spinal cord injury with spinal shock. If the reflexes are normal in a clinically weak limb, a diagnosis other than Guillain–Barré syndrome should be entertained.

Although sensory symptoms do not classically constitute a primary complaint in Guillain–Barré syndrome, severe pain is frequent. In the acute phase, pain may be nociceptive due to inflammation. In a prospective study of 55 patients with Guillain–Barré syndrome, 89.1% reported pain and half had distressing pain [44]. Aching back and leg pain was common and resolved over the first 8 weeks, likely reflecting inflammatory polyradiculopathy. Limb pain is also common and is frequently more prolonged. In the chronic phase of recovery, pain may be due to axonal loss and possible regeneration of sensory fibers [21]. Meningismus, muscle, joint, and visceral pain have also been described [45]. Overall, the severity of pain is not associated with the severity of motor weakness and respiratory involvement.

Autonomic neuropathy is also common in Guillain–Barré syndrome, including both sympathetic and parasympathetic abnormalities. The majority of patients have some degree of autonomic dysfunction, and in severe cases, sudden autonomic failure may result in death. Autonomic symptoms include cardiac arrhythmias, labile blood pressure, abnormal hemodynamic responses to drugs, bowel and bladder dysfunction, pupillary abnormalities, and sweating changes [46]. Routine monitoring of cardiovascular status and careful use of short-acting hemodynamic medications are advised. While it is difficult to predict which individual patient will have a dramatic autonomic involvement, those with axonal variants and greater disease severity are at greater risk. One study reported a correlation between reduced intraepidermal nerve fiber density and development of autonomic instability [47].

Recovery is often slow, over weeks to months. Prognosis is generally good with few cases of true recurrence, not including those with an eventual diagnosis of CIDP or worsening of symptoms after initial treatment. Table 12.2 lists factors that affect prognosis. Poor outcomes are associated with increased age, preexisting cardiac or pulmonary disease, rapid progression of Guillain–Barré syndrome symptoms, axonal variants, and autonomic instability. Mortality remains around 3–8% even with aggressive supportive care in developed countries [48]. Causes of death include complications of critical illness, such as ventilator-associated infections, pulmonary embolism, and autonomic dysfunction causing cardiac arrhythmias [49]. Roughly 80% of patients recovery completely or have only subclinical abnormalities, such as hyporeflexia, or electrodiagnostic evidence of denervation. About 5–10% of the patients have severe residual weakness. The pace and degree of recovery are often influenced by the severity and rapidity of onset and the degree of axonal involvement, as axonal regeneration is

Table 12.2 Various factors affect prognosis in Guillain–Barré syndrome

Factors in Guillain–Barré syndrome affecting prognosis
Patient demographics
Worse: Greater than 50 or 60 years of age
Comorbid cardiac or pulmonary disease
Associated antecedent infections
Worse: Preceding diarrheal (instead of respiratory) illness
CMV
Better: EBV
Clinical features
Worse: Rapid onset and progression at presentation
Need for artificial ventilation
Infectious complications of critical illness
Axonal variants
Autonomic dysfunction
Better: Miller Fisher variant without significant overlap with Guillain–Barré syndrome
Chinese paralytic syndrome (subset of AMAN)
Electrodiagnostic features
Worse: Signific ant axonal loss
CMAP less than 20% of normal [129]

Age is usually the predominant factor in predicting prognosis in Guillain–Barré syndrome, presumably related to the reduced ability for nerve repair and regeneration. Immunologic differences and comorbid conditions may also contribute. Axonal pattern and antecedent infections have a worse prognosis. Respiratory or autonomic dysfunction affects mortality and morbidity in the acute phase.

much slower than remyelination. Associated infection also can influence prognosis. Antecedent diarrheal illness with *C. jejuni* is associated with delayed recovery [50]. CMV infection is also associated with prolonged recovery, while EBV is associated with a milder disease and better prognosis [51]. Fatigue can be a disabling symptom even in patients with good motor recovery. Fatigue may be due to incomplete mild residual weakness not appreciable on clinical exam. However, the etiology of fatigue, which is quite common (60–80%), is not known [52, 53].

Guillain–Barré Syndrome in Children

Guillain–Barré syndrome occurs in infants and children at a lower rate than in adults, about 0.8 per 100,000 per year [54]. While the clinical features of Guillain–Barré syndrome in children are similar to adults, there are important differences. Infants or small children may present with hypotonia, feeding difficulties, irritability due to pain, and reduced activity, which may initially suggest altered mental status in children. Proximal muscle and cranial nerve involvement are more common, occurring in an estimated 30–45% of children [55, 56]. Another major clinical difference is the shorter course of disease [55]. Most cases reach nadir by 2 weeks and there is often little residual deficits by 4 months. Long-term residual deficits are rare and usually mild. More than 90% of patients completely recover [57]. Mortality rate is also lower, about 1–2%, due to respiratory and autonomic cardiovascular complications [58].

Clinical Variants

Acute Inflammatory Demyelinating Polyradiculoneuropathy

AIDP is the most common form in Europe and North America, and the clinical features described above pertain primarily to it. Often it is difficult to differentiate AIDP from axonal variants without electrodiagnostic testing. However, AIDP in general has a better prognosis due to a relatively shorter time required for remyelination versus axonal regeneration.

Axonal Variants (AMAN, AMSAN)

Axonal variants of Guillain–Barré syndrome have been recognized since 1986 [59]. The evidence for predominant axonal involvement is the electrodiagnostic pattern of significantly reduced motor and/or sensory action potential amplitudes without conduction slowing or prolonged latency. There may also be early prominent electromyographic evidence of denervation. Autopsy studies of several of these patients have confirmed axonal degeneration as the primary pattern [60]. Since the recognition of axonal Guillain–Barré syndrome as a clinical entity, this pattern has been classified into two categories depending on the presence of sensory involvement. Acute motor axonal neuropathy (AMAN) refers to axonal Guillain–Barré syndrome without sensory involvement and acute motor and sensory axonal neuropathy (AMSAN) refers to those with sensory involvement. Both axonal versions are more common in Asia and Central and South America.

An outbreak of axonal motor neuropathy occurred in northern China in 1991 and was associated with *C. jejuni* infections [7]. These patients had a rapid decline in strength, but also relatively rapid recovery with complete resolution of symptoms over time. Electrophysiology studies and autopsy results demonstrated predominant axonal injury with little evidence of demyelination; thus, they were referred to as AMAN [7, 60]. They are distinct from cases of acute motor and sensory axonal neuropathy which have a much more prolonged course with often significant residual deficits [59]. The difference in prognosis is thought to be due to distal conduction block in the Chinese AMAN cases compared to widespread axonal degeneration in acute motor and sensory axonal neuropathy.

Axonal variants in general have a worse prognosis, including both AMSAN and AMAN (with the exception of the Chinese outbreak). There is more rapid progression with slower and incomplete recovery, as well as a greater likelihood of respiratory weakness requiring mechanical ventilation and autonomic involvement. The pathophysiology of these variants is described in the prior section. Again, there are often corresponding antiganglioside antibodies associated with these conditions (see Table 12.1).

Cranial

Miller Fisher syndrome is the most commonly recognized cranial nerve variant of Guillain–Barré syndrome. The classic triad includes ataxia, areflexia, and ophthalmoplegia [61]. All of these symptoms do not have to be present simultaneously for the diagnosis. Varying degrees of limb weakness, paresthesias, and autonomic dysfunction may also exist and there may be overlap syndromes between the Miller Fisher variant and classic AIDP [62]. Complete recovery of symptoms in the Miller Fisher syndrome is the rule [63] and immunomodulatory therapies are controversial in these patients given the eventual spontaneous recovery. Antibodies to GQ1b are present in over 90% of the patients with Miller Fisher syndrome and other antibodies may also exist, as well as additional antibodies in the overlap syndrome (see Table 12.1) [64].

A pharyngeal–cervical–brachial variant of Guillain–Barré syndrome has also been reported. As the name implies, bulbar dysfunction is common and early in this variant. Neck and shoulder weakness is greater than leg weakness. Facial and extraocular muscle weakness, and ataxia can also occur, signifying an overlap with Miller Fisher syndrome. Leg weakness may be mild or severe, and if relatively spared, there may be preservation of deep tendon reflexes. Along with the "descending" pattern of weakness in the case, the preserved reflexes in the legs may cause diagnostic confusion. This variant was first described in three patients in 1986 [65]. Among 100 patients with this variant, *C. jejuni* infection preceded weakness in 31%, half had antibodies to GT1a and 30–40% to GQ1b, GM1, GM1b, GD1a, or GalNAc-GD1a [66]. This observation suggests there is overlap between other variants of Guillain–Barré syndrome and the pharyngeal–cervical–brachial variant, supporting the concept that these disorders exist on a clinical continuum with specific physiologic and anatomic variation determined by the specific immune response.

Central Nervous System Involvement

Bickerstaff's encephalitis is a variant of Guillain–Barré syndrome characterized by central nervous system involvement. Symptoms usually start with cranial nerve or limb weakness and later

progress to disturbance of consciousness, which can lead to coma. Extensor plantar responses may be seen despite an otherwise flaccid paresis in the limbs, further indicating both central and peripheral involvement. In a study of 62 cases, positive anti-GQ1b antibodies were found in 66% of the patients [67]. On autopsy, there was evidence of CNS inflammation with lymphocytic infiltrates as well as axonal degeneration in the peripheral nerves. An awareness of Bickerstaff's encephalitis is important when evaluating patients with acute mental status changes as immunomodulatory therapy may hasten recovery. However, most patients have a monophasic course with significant recovery similar to the majority of Guillain–Barré syndrome cases. Morbidity and mortality is due to complications of critical illness and autonomic dysfunction.

Diagnosis

The diagnosis of classic Guillain–Barré syndrome is usually not difficult. The diagnosis is clinical, with ancillary testing supporting the diagnosis rather than defining it. The clinical features described above with an awareness of the broad spectrum of clinical presentations are helpful in the identification of less common variants. Cerebrospinal fluid (CSF) examination and electrodiagnostic testing are helpful in confirming the diagnosis of Guillain–Barré syndrome. However, CSF and electrodiagnostic tests are often normal early in the disease, and their sensitivity changes with disease progression. Therefore, treatment often must be initiated based on clinical judgment prior to development of unequivocal CSF or electrodiagnostic abnormalities. This is particularly true for patients with rapid progression of symptoms where early therapy may be critical.

CSF Testing

Albuminocytologic dissociation (elevated CSF protein concentration in the absence of pleocytosis) is a hallmark of Guillain–Barré syndrome. Cerebrospinal fluid is often normal in the first week, and becomes abnormal in greater than 90% of patients by the end of the second week of symptoms [68]. In a large case series of Miller Fisher syndrome, only a quarter of patients had elevated CSF protein concentrations in the first week, whereas 84% had an elevated CSF protein concentration by the third week [69]. Therefore, early absence of increased CSF protein concentration does not preclude the diagnosis.

An elevation in the CSF cell count, especially with a predominance of polymorphonuclear leukocytes, suggests an alternative diagnosis. These include infectious diseases, such as Lyme disease, HIV, CMV, EBV, or leptomeningeal malignancy. However, there have been reports of cases fulfilling Guillain–Barré syndrome diagnostic criteria with a CSF pleocytosis. One study reported five cases of rapidly progressive Guillain–Barré syndrome with CSF cell counts of greater than 50/WBC/mm^3 [70]. Notably, all patients died from 4 to 100 days after onset and autopsy demonstrated demyelinating polyradiculitis. Immunohistochemical stains for HSV, CMV, EBV, VZV, enteroviruses, tick-borne encephalitis virus, and spirochetes were negative. The authors concluded that CSF pleocytosis and PMN predominance may be seen, although this is atypical, and the clinical course is different from typical Guillain–Barré syndrome. A thorough search for infectious, neoplastic, or other autoimmune etiologies should be done when there is significant elevation in the CSF cell count.

Electrophysiology

Electrophysiology aids in the classification of Guillain–Barré syndrome into demyelinating and axonal types (Table 12.3). Nerve conduction studies were abnormal in 87% of patients within 5 weeks of symptom onset, while 10% had indeterminate evaluations [71]. In the early phase of the disease, because of the patchy nature of nerve or root involvement, diagnostic criteria may not be fully met. Repeating the study in atypical cases after 1–2 weeks when an early study is normal or indeterminate can be useful. Earliest changes include minimal F wave latency prolongation. Conduction block is also an important feature of acquired demyelination, but may be proximal and

Table 12.3 Electrodiagnostic criteria for Guillain–Barré syndrome

Electrodiagnostic criteria for Guillain–Barré syndrome and subtypes
AIDP At least one of the following in each of at least two nerves, or at least two of the following in one nerve if all others inexcitable and dCMAP > 10% LLN: • Motor conduction velocity <90% LLN (85% if dCMAP < 50% LLN) • Distal motor latency >110% ULN (>120% if dCMAP <100% LLN) • pCMAP/dCMAP ratio <0.5 and dCMAP >20% LLN • F-response latency >120% ULN
AMSAN None of the features of AIDP except one demyelinating feature allowed in one nerve if dCMAP < 10% LLN Sensory action potential amplitudes < LLN
AMAN None of the features of AIDP except one demyelinating feature allowed in one nerve if dCMAP < 10% LN Sensory action potential amplitudes normal
Inexcitable dCMAP absent in all nerves or present in only one nerve with dCMAP < 10% LLN

dCMAP compound muscle action potential amplitude after distal stimulation; *pCMAP* compound muscle action potential amplitude after proximal stimulation; *LLN* lower limit of normal; *ULN* upper limit of normal.
In AIDP variant, velocity and latency are predominantly affected with relative preservation of amplitudes, producing a demyelinating pattern. The axonal variants are defined by the absence of demyelinating features and loss of amplitude. This is seen only in motor responses in AMAN, and in both motor and sensory responses in AMSAN. Sometime the injury is so severe that no response can be obtained; it is not classifiable as primarily axonal or demyelinating.
Adapted from Hughes [2], with data from Hadden [130] and Ho [131].

difficult to elicit. One study reported conduction block in 10% of patients [72]. Motor conduction abnormalities occur first, followed by sensory conduction changes. In AIDP, axonal features develop later with reduced sensory nerve and compound muscle action potential amplitudes and fibrillations and positive sharp waves on needle electromyography. Electrodiagnostic assessment for axonal loss may assist in prognostication; those with prominent axonal loss take longer to recover and are more likely to do so incompletely [73]. In cases where nerve conduction responses are absent or of markedly reduced amplitude, it may be challenging to characterize the primary process as demyelinating or axonal.

Another feature that may be seen on electrophysiological study in Guillain–Barré syndrome is referred to as "normal sural-abnormal median pattern." This is often observed in early stages before the development of other nerve conduction abnormalities. This pattern of reduced median sensory response with relative preservation of sural response is seen more frequently in inflammatory neuropathies (AIDP and CIDP), compared to diabetic neuropathy, motor neuron disease, or control groups [74]. The extreme of normal sural amplitude with absent median response is only seen in AIDP or CIDP.

In the Miller Fisher variant, sensory nerve conduction studies may be abnormal even in the absence of limb symptoms [75]. Sensory loss may contribute to ataxia. Motor nerves are less commonly or severely affected, except in cases of overlap syndromes. There have been conflicting reports on whether the sensory nerve abnormality is primarily demyelinating [76] or axonal [77, 78]. Proximal facial nerve conduction abnormality has also been described, with predominantly demyelinating features [79].

Etiology and Differential Diagnosis Studies

In some circumstances, diagnostic studies for associated infections may help with prognosis (detailed in "Clinical Features" section regarding prognosis). In antecedent diarrheal illness or a clinical picture of AMAN, stool culture and serology for *C. jejuni* should be obtained. Other infectious disease diagnostic studies include acute and convalescent serologies for CMV, EBV, and *M. pneumoniae*. Antiganglioside antibodies can also be obtained, especially in situations of uncertain diagnosis. For example, positive anti-GQ1b is sensitive and specific for Miller Fisher variant and overlap syndromes. However, these tests often take several days or more, so immunomodulatory therapy generally must be initiated presumptively.

Table 12.4 Signs and measures of respiratory distress

Signs and measures of respiratory distress
Warning signs
• Bulbar weakness with dysphagia, dysphonia
• Rapid shallow breathing
• Tachycardia
• Weak cough
• Staccato speech
• Accessory muscle use
• Abdominal paradox
• Orthopnea
• Weakness of trapezius and neck muscles
• Single breath count less than 20
• Cough after swallowing
Objective assessment
• Desaturation or nocturnal desaturation
• Forced vital capacity <15 mL/kg, or <1 L, or a 50% drop from previous
• Maximum inspiratory pressure >−30 cm H_2O
• Maximum expiratory pressure <40 cm H_2O

Recognizing these clinical signs and symptoms of pending respiratory failure is required to anticipate the need for mechanical ventilation and prevent cardiopulmonary arrest in Guillain–Barré syndrome. Initial and subsequent scheduled objective measurements of pulmonary function with bedside spirometry can follow respiratory progress in Guillain–Barré syndrome.
Adapted from Mehta [80].

Supportive Care Studies

Beyond studies to diagnose Guillain–Barré syndrome, other studies are needed to aid in supportive care. In admitted or critically ill patients, comprehensive chemistry panel, complete blood count, coagulation studies, and urine analysis are helpful to establish a baseline and can be followed as needed. Given the prominence of autonomic features, baseline ECG should be obtained and continuous cardiac and hemodynamic monitoring are needed if the patient is symptomatic, is critically ill, or has abnormalities on initial screening. Respiratory assessment requires a chest X-ray and pulmonary function testing. Signs and measurements of respiratory distress signifying the necessity of noninvasive respiratory support or mechanical ventilation are listed in Table 12.4 [80].

Differential Diagnosis

Weakness may be a symptom originating from any part of the nervous system. Localization along the neuroaxis remains the first step in assessment of the patient. The distribution of weakness (hemiparesis vs. paraparesis), tone, and reflexes differentiates between central and peripheral processes. Once localized to the peripheral nervous system, the presence or absence and distribution of sensory symptoms and reflex changes help to distinguish between a root or nerve lesion versus a motor neuron, neuromuscular junction, or muscle disorder.

Table 12.5 lists other causes of acute weakness, including both central and peripheral nervous system disorders that can mimic Guillain–Barré syndrome.

When clinical localization is to the lower motor neuron or more peripheral, laboratory studies can help differentiate between different causes of acute polyneuropathies. When involvement is restricted to the lower motor neuron, stool culture for polio (in relevant geographic areas) and West Nile virus CSF IgM should be obtained [81]. Nonpolio enteroviruses may cause an acute flaccid paralysis. Send CSF enteroviral PCR and CSF viral culture in suspected cases. Because of lower motor neuron involvement, weakness predominates over sensory symptoms, unless there is a concurrent myelitis. In acute neuropathies, drug, toxin, heavy metal screen, urine porphobilinogen and delta-aminolevulinic acid concentrations and inflammatory markers for vasculitis (ESR, ANA, ENA, ANCA, cryoglobulins, etc.) can be obtained in the appropriate clinical settings [82].

There are several infectious causes of polyradiculopathy that may mimic Guillain–Barré syndrome (Table 12.6). HIV seroconversion may present similarly to AIDP, but often with CSF pleocytosis. In the seroconversion state, serology using Western blot may not always be positive and PCR for viral load may be needed. Neuroborreliosis can present with meningitis and

Table 12.5 Differential diagnosis of acute flaccid paralysis by site of involvement in the neuroaxis

Differential diagnosis of acute flaccid paralysis
Central nervous system
Brainstem stroke or encephalitis
Myelopathy—trauma, transverse myelitis, space-occupying lesions
Motor neuron
Poliomyelitis
Nonpolio enteroviruses
West Nile virus poliomyelitis-like syndrome
Peripheral root or nerve
Guillain–Barré syndrome
Diphtheritic neuropathy
Acute intermittent porphyrias
Vasculitic neuropathy
Critical illness neuropathy
HIV seroconversion radiculomyelitis
Neuroborreliosis
Lymphomatous neuropathy
Intoxications: heavy metals, hexane
Tick paralysis
Neuromuscular junction
Myasthenia gravis, including drug-induced or exacerbated MG
Botulism
Organophosphate poisoning
Muscle
Hypokalemia
Hypophosphatemia
Periodic paralysis
Rhabdomyolysis
Inflammatory myopathy
Critical illness myopathy

There are central and peripheral causes of acute flaccid paralysis and localization helps to narrow down the differential diagnosis.

polyradiculopathy, mimicking Guillain–Barré syndrome, and should be considered in the differential diagnosis. Similar to HIV polyradiculopathy, CSF pleocytosis is common. Diphtheria can also present with polyradiculopathy, but usually with bulbar onset and predominance (98% compared to 10% in Guillain–Barré syndrome), with relatively minor limb involvement [82]. The neuropathy seen with diphtheria also shows demyelinating features on electrophysiology. Preceding sore throat may mimic antecedent infections in Guillain–Barré syndrome. Respiratory dysfunction is common and mechanical ventilation may be needed in 20% of patients with diphtheria. The clinical course is prolonged, with a continued deterioration over 1–2 months as well as a common biphasic course with secondary worsening. Overall mortality and residual morbidity are much higher than in Guillain–Barré syndrome [83].

Tick paralysis is another cause of acute flaccid paralysis. Following a tick bite, there is usually symmetrical ascending weakness which can progress for hours to days after the tick is removed. There have been descriptions of more localized weakness. In most cases, weakness improves spontaneously after the tick is removed, over hours in cases involving North American species and days in Australian species. Sensory disturbances can also occur. The pathophysiology of tick paralysis is unclear, but sodium channel dysfunction causing conduction block and neuromuscular abnormalities have been theorized [84, 85]. A careful evaluation for ticks is essential in cases of acute flaccid paralysis, especially in children under 10 years of age and people with recent outdoor exposures in endemic areas.

Neuromuscular junction disorders may cause acute weakness. In infants and toddlers, botulism causes weakness associated with autonomic features, including constipation and pupillary dilation. The constellation of symptoms should prompt testing for botulism in stool samples and electrophysiological testing for a presynaptic defect. Fortunately, Guillain–Barré syndrome is relatively rare in infants, but should still be considered in infants with acute weakness. In adults, abrupt presentation of undiagnosed myasthenia gravis is possible. Sensory features are not seen in myasthenia and may help to differentiate from Guillain–Barré syndrome.

When the presentation is a pure sensory syndrome, Guillain–Barré syndrome is unlikely. Significant sensory loss including proximal limbs and trunk usually indicates a sensory neuronopathy. Causes include paraneoplastic syndrome with anti-Hu antibodies and neuronopathy associated with Sjogren's disease. There have been a handful of reports of Guillain–Barré syndrome-like syndromes with predominant sensory involvement and no clinical weakness. However, electrodiagnostic testing still showed abnormality

Table 12.6 Distinguishing features of Guillain–Barré syndrome and mimickers

Syndrome	Pattern of involvement	Laboratory abnormalities	Electrodiagnostic abnormalities	Other features
Guillain–Barré syndrome	Symmetrical, distal and proximal, motor > sensory, autonomic	CSF cell count is nl ↑ CSF protein	Demyelination or axonal on NCV in sensory and motor nerves	Antecedent infection
Poliomyelitis	Motor: leg > arm > bulbar, asymmetric myalgia, hyperesthesia, autonomic	↑CSF cell count ↑CSF protein	Normal sensory, low amplitude motor conduction	2–5 days postinfection
West Nile	Motor unless myelitis with sensory changes, asymmetric, often with encephalitis	↑CSF cell count ↑CSF protein—send CSF IgM	Normal sensory, low amplitude motor conduction	Some AIDP-like syndromes also
HIV seroconversion radiculoneuropathy	Similar to Guillain–Barré syndrome	↑CSF cell count ↑CSF protein—send serology and CSF viral load	Demyelination or axonal on NCV in sensory and motor nerves	Check viral load in early phases of seroconversion
Acute *B. burgdorferi* polyradiculoneuropathy	Cranial nerves (facial), concurrent meningitis, pain, weakness, minimal sensory loss	↑CSF cell count ↑CSF protein—send serum and CSF IgG	Axonal pattern	1–2 months postinfection
Diphtheria	Bulbar, prolonged/biphasic course, autonomic	CSF cell – +/–, CSF protein – +/–, elevated pressure	Demyelinating pattern with prolonged latency, reduced velocity	Systemic infection with multiorgan failure
Tick paralysis	Ascending motor >> sensory, autonomic	CSF-nl	Conduction block, reduced amplitude, normal velocity, RNS-nl	
Botulism	Motor only, early constipation, pupillary dilation	CSF-nl	Presynaptic NMJ defect, small CMAP	
Myasthenia gravis	Motor only	CSF-nl	Postsynaptic NMJ defect	

CSF cerebrospinal fluid, *NCS* nerve conduction study, *RNS* repetitive nerve stimulation, *NMJ* neuromuscular junction, *CMAP* compound motor action potential.
Common mimickers of Guillain–Barré syndrome are listed in this table with characteristic patterns of involvement, typical CSF results, and electrodiagnostic abnormalities. Guillain–Barré syndrome remains a clinical diagnosis based on pattern of involvement that is distinguished from these other syndromes. Ancillary testing can help confirm the diagnosis.

in motor nerve conductions [86]. Therefore, it may be possible to have very little clinical weakness in Guillain–Barré syndrome, but electrophysiologically there is still motor involvement. In contrast, patients with sensory neuronopathies have normal motor conduction studies. Electrophysiology is helpful in clarifying rare atypical cases of Guillain–Barré syndrome with only subclinical motor involvement.

Treatment

The treatment in Guillain–Barré syndrome consists of two main approaches. The first is immunologic therapy to alter disease process, hasten recovery, and improve neurological outcome. The second is supportive care for patients while recovery takes place.

Immunomodulatory Treatment

Plasma Exchange

The efficacy of plasma exchange was first reported in case studies in 1978 [87]. A series of randomized controlled trials of plasma exchange subsequently showed benefit compared to supportive care alone. Overall, plasma exchange has a notable benefit when used in patients with moderate to severe disease [88–93]. Most of the studies treated patients within 2 weeks of onset of weakness, with one study treating within 1 month. Most patients also had moderate to severe impairment, as defined by an inability to walk without assistance. There is significant improvement in the Guillain–Barré syndrome severity score at 1 month after 3–8 plasma exchanges, as well as the percentage of patients who are able to ambulate independently. There was a shortened hospital stay in the treated group (48.4 days vs. 53.0 days) in one study, as well as reduced ventilator dependence (11.7 days vs. 15.3 days) [89].

The French Cooperative Group looked at 304 adults with Guillain–Barré syndrome who were unable to ambulate and randomized them to receive four versus two sessions of plasma exchange. There was significant improvement in days to ambulation with assistance (20 vs. 24), days needing ventilatory support (15 vs. 37), days to hospital discharge (21 vs. 26), and proportion of full recovery at 1 year (64% vs. 48%) in the group that received four exchanges [94]. This overall pattern was also seen in the mildly affected group receiving two exchanges compared to the control group, but only a trend toward greater improvement in the severely affected group (mechanically ventilated) receiving six exchanges compared to four. There was an increase in adverse events in the six exchange group. Based on these data, four exchanges were recommended for patients with moderate to severe disease, and two for patients with mild disease. Many clinicians continue to use five exchanges, particularly in those with rapidly progressive disease or severe weakness.

Adverse effects of plasma exchange include infections, labile blood pressure, cardiac arrhythmias, line complications, and pulmonary embolus. However, in the three studies where these complications were well documented, they did not occur more frequently than with the control group [90, 93, 94].

Intravenous Immune Globulin

By the time Intravenous immune globulin (IVIG) was systematically studied, plasma exchange had already become the standard of care in adults with Guillain–Barré syndrome. No placebo-controlled studies are available in adult patients. However, several studies comparing IVIG to supportive treatment in children demonstrated significant hastening of recovery in those treated with IVIG [95–97].

Most of the studies compare the effects of IVIG with plasma exchange, and have found equivalence in multiple outcome measures similar to those in the initial plasma exchange studies [98–101]. One study reported a slight trend toward decreased relapse rate in those treated with IVIG compared to plasma exchange, but the result was not statistically significant [98, 101]. There was also no significant difference between IVIG alone vs. IVIG after plasmapheresis [101]. The dose of IVIG used in these trials was 0.4 g/kg daily for 5 days. One pediatric study comparing

this dose to 1.0 g/kg for 2 days did not find any difference in outcome although there was a slight increase in early relapse in the 2-day regimen (0/23 in 5-day course and 5/23 in 2-day course, $p=0.049$) [97]. The suggestion of an increased risk of early "relapse" may have been due to treatment-related fluctuations in patients whose IVIG course was completed soon after presentation. This issue is explored more completely below. Many clinicians favor administering the 2 g/kg dose over 2 days when possible.

IVIG complications are less common than complications with plasma exchange. Adverse events include nausea and vomiting, aseptic meningitis, exacerbation of chronic renal failure, thrombotic complications, and painful erythema at the infusion site [101]. Due to the relative fewer complications and the ease of administration compared with plasma exchange, IVIG has become the first-line treatment in Guillain–Barré syndrome.

Steroids

Oral or intravenous steroids have not shown benefit in the treatment of Guillain–Barré syndrome. Based on inflammatory and immune-mediated pathology of Guillain–Barré syndrome, steroids have been tried as early as the 1950s [102]. There have been six controlled trials: four studies showed slower recovery with oral steroids and two studies showed a nonsignificant trend toward faster recovery with intravenous methylprednisolone, further supported by Cochrane meta-analysis [103–109]. Another trial evaluated intravenous methylprednisolone plus IVIG versus IVIG alone and found that there was a slightly greater proportion of patients who improved one point on the disability scale in 4 weeks, but this did not translate to any difference in ambulatory ability at 8 weeks or time to walking independently [107]. The available evidence shows slower recovery with oral steroids and little evidence for efficacy with intravenous steroid treatment in Guillain–Barré syndrome.

Timing

Most randomized controlled trials for Guillain–Barré syndrome begin treatment within 2 weeks of symptom onset in moderate to severe disease (loss of independent ambulation). Some trials initiated treatment within 4 weeks of onset and still showed benefit with treatment. No trial has looked at timing of treatment in patients with severe upper extremity, bulbar, or pulmonary weakness or severe manifestation of Miller Fisher syndrome, but early treatment seems appropriate in those with significant dysfunction.

Mildly Affected Patients

The French Cooperative study looked at mildly affected patients who remained ambulatory and found there was a greater proportion of patients with faster rate of motor recovery in the plasma exchange group [98]. However, if the patient presents at close to nadir (3–4 weeks after onset) and still has only mild manifestations, it can be argued that treatment may not be necessary. However, residual symptoms, though mild, can interfere with functional ability. Individual assessment should be made in each case. Miller Fisher variant without overlap syndrome is generally a self-limited disease with mostly complete recovery. If symptoms are not severe enough to cause significant discomfort or dysfunction, treatment may not be necessary.

Repeat Treatments

A second course of therapy is often considered in patients with recrudescence of symptoms or in those with severe disease for whom treatment was initiated very early. Figure 12.2 [110] depicts the course of Guillain–Barré syndrome along with titers of antiganglioside antibodies and the effect of IVIG. Deterioration may occur if antibody titers remain elevated after the effects of the first course of IVIG (or plasma exchange) has waned. One small uncontrolled study evaluated a second course of IVIG and found it to be effective [111]. Four patients who did not improve further at 14–21 days after initial IVIG treatment were given a repeat course and improvement was noted within days. Two patients had demyelinating features and the other two had axonal damage. In clinical practice, a repeat course of therapy

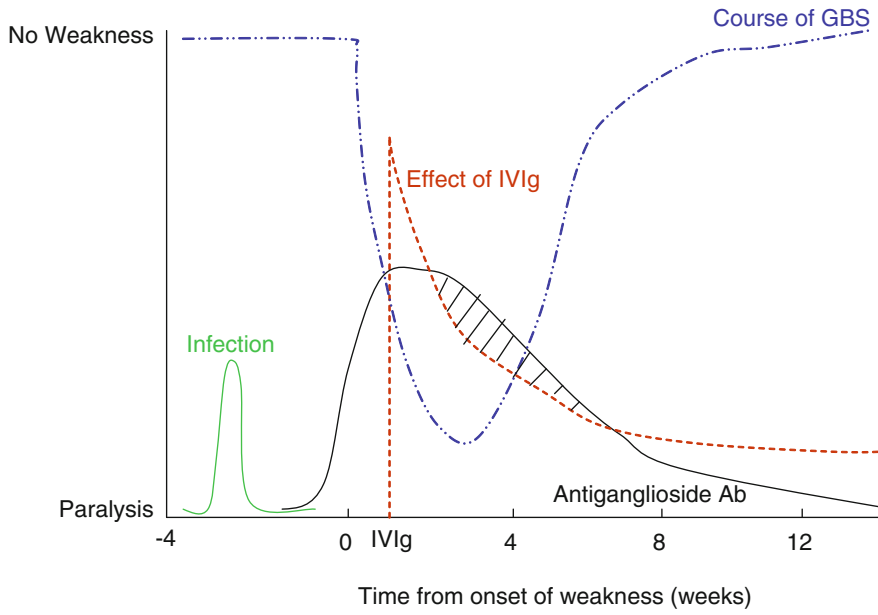

Fig. 12.2 This figure shows changes of antibody titers in Guillain–Barré syndrome. Superimposed is effect of IVIG. If antibody titers are still elevated after treatment (*shaded area*), further clinical deterioration may occur which would be considered as treatment-related fluctuation. Further treatment course may help to reduce antibody titers and mitigate the symptoms. Adapted from van Doorn [21], superimposed with the pharmacokinetics of IVIG on immunoglobulin levels (data from Bonilla [110])

is often given if symptoms worsen following initial therapy, particularly if it is during a time frame where continued antibody production is possible. Because of this theoretical concern, a repeat IVIG treatment may be administered 1–2 weeks after the first course if treatment was initiated within the first days of illness.

A closely related issue is that of "treatment-related fluctuations." Treatment-related fluctuation (GBS-TRF) is defined as deterioration after initial improvement or stabilization of symptoms within 2 months of onset, which occurs in 8–16% of Guillain–Barré syndrome patients [112–114]. Guillain–Barré syndrome recurrences are distinct episodes of symptoms with complete clinical recovery separated by 2 months or by 4 months if recovery is incomplete. This differs from CIDP in that patients often have a long asymptomatic period with normalization of deep tendon reflexes without treatment. Some cases of what appears to be GBS-TRF may actually be CIDP, as the symptoms recur in between IVIG treatments and require further chronic immunosuppressive therapies. Acute presentation of CIDP may occur in up to 20% of the cases, but compared to true Guillain–Barré syndrome, there is often less associated antecedent infection, facial weakness, respiratory complications, and autonomic dysfunction [115]. The diagnosis of acute onset CIDP should be considered when a patient deteriorates after 9 weeks from onset or when deterioration occurs three times or more [116]. Table 12.7 lists differences between GBS-TRF, recurrent Guillain–Barré syndrome, and acute onset CIDP. However, in the first 4 weeks of presentation, it may be impossible to fully differentiate between these entities and revision of the diagnosis is needed if the symptoms progress despite treatment or over a time course different from typical Guillain–Barré syndrome.

Another situation where repeat treatment is sometimes considered is for patients with severe disease who are not improving. While it is often tempting to administer another course of IVIG or plasma exchange in patients with severe disease who are not improving after several weeks, in the absence of a clear progression of symptoms, there are presently no data to support this practice.

Table 12.7 Comparison between Guillain–Barré syndrome treatment-related fluctuation (TRF), recurrence, and acute onset chronic inflammatory demyelinating polyradiculoneuropathy (A-CIDP)

	GBS-TRF	Guillain–Barré syndrome recurrence	A-CIDP
Time to worsening	<2 months	>2 months	Several months
Time to nadir	8 days		26 days
Number of TRF or exacerbation within 2 years from onset	≤2		≥3
Guillain–Barré syndrome disability score (Hughes) at nadir	≥3, overall more severe		Broad range, overall more mild

This is based on data extracted from Liselotte et al. [116], and represents a statistical analysis of the difference in timing, number of exacerbation, and severity that may aid in differentiating between these entities.

Emerging Therapies

A number of monoclonal antibodies may have potential for the treatment of Guillain–Barré syndrome and its variants. Eculizumab has been used to block complement activation in a murine model of Miller Fisher syndrome with anti-GQ1b antibodies. Eculizumab blocks the formation of human C5a and C5b-9 and prevented electrophysiological and structural abnormalities at the anti-GQ1b antibody preincubated neuromuscular junction in vitro. Injection of eculizumab in mice with respiratory failure and neuropathy induced by intraperitoneal injection of anti-GQ1b prevented disease manifestations [117]. Rituximab was also found to be efficacious in one case report of Guillain–Barré syndrome following allogeneic hematopoietic stem cell transplant for myelodysplastic syndrome [118]. However, tumor necrosis factor inhibitors, such as infliximab, etanercept, and adalimumab, have been found to possibility induce Guillain–Barré syndrome–like syndromes when used for treatment of rheumatologic diseases [119]. Further research is needed before monoclonal antibodies become a validated treatment for Guillain–Barré syndrome.

Immunoabsorption has also been tried in Guillain–Barré syndrome treatment. A case report described benefit of immunoabsorption targeted against IgG and IgM GM1 antibodies following *C. jejuni* infection in a 12-year-old boy [120]. Another case report described immunoabsorption in a severe case of Guillain–Barré syndrome with antigalactrocerebroside IgM antibody following *M. pneumoniae* infection [121] after failure to respond to IVIG. Immunoabsorption has the advantage of not needing pooled blood products like plasma exchange (fresh frozen plasma) or IVIG (immunoglobulins), and may reduce allergic reactions and, theoretically, blood-borne infections. In the two cases, 2 Lof plasma was treated at a time and a large bore intravenous line was not required, which may minimize the risk of central line complications. It appears that immunoabsorption may eventually have a role in patients with specific antiganglioside antibodies that are unresponsive to the standard treatments.

Symptomatic Treatment

General supportive measures for patients with Guillain–Barré syndrome include assessment of respiratory and cardiovascular status, bulbar, bowel and bladder dysfunction and pain. These will be further discussed below. Prevention of deep vein thrombosis and pulmonary embolism is important due to reduced mobility and possible increased thrombotic risk with immunomodulatory therapies. Prevention of infections, decubitus ulcers, and contractures are other aspects of supportive care.

Respiratory Support

Respiratory support is the most important emergency treatment in severe neuromuscular weakness. About 25% of Guillain–Barré syndrome patients with inability to walk independently will need ventilatory support [2]. Adequate support begins with accurate assessment of respiratory

status. Clinical signs and parameters of respiratory distress are listed in Table 12.4. All patients with Guillain–Barré syndrome should have baseline pulmonary function tests for forced vital capacity and maximum inspiratory and expiratory pressures. In patients with a rapid progression of weakness prior to presentation, inability to walk unaided on presentation, and/or with significant bulbar weakness, pulmonary function should be obtained at regular intervals. The decision to institute mechanical ventilatory support is primarily clinical. Along with clinical judgment, when respiratory parameters fall near or below those listed in Table 12.4, ventilatory support should be considered. Often times, the trend in values is more telling than the absolute number. Arterial blood gases can be useful in assessment of a patient's respiratory status, but are often a delayed indication of respiratory distress in the setting of neuromuscular weakness. Arterial blood gas may be normal in patients with severe respiratory weakness that may already require intubation. Patients with established respiratory failure from neuromuscular weakness will show hypoxemia and a compensated respiratory acidosis (raised $PaCO_2$ and bicarbonate with a normal or mildly reduced pH). Elevations of the pH and bicarbonate with normal PaO_2 and $PaCO_2$ suggest nocturnal hypoventilation. Once the patient is intubated, pulmonary function should be monitored for potential weaning and extubation. Predictors of successful extubation include negative inspiratory force less than −50 cm H_2O and vital capacity improvement greater than 4 mL/kg from preintubation value [122]. Tracheotomy should be considered after 2 weeks of intubation, especially if parameters do not improve from baseline.

Autonomic Support

A baseline ECG should be obtained in all patients. Initial continuous monitoring of rhythm and hemodynamic parameters is indicated as the course of progression is often uncertain at presentation. Further continuous monitoring is required in patients with signs of autonomic dysfunction and those with a rapid course and severe disease. Atropine can be used for brachycardia. Transcutaneous pacemaker may be necessary for patients with second- or third-degree symptomatic heart block. If there is symptomatic hemodynamic instability, short-acting agents for treatment should be selected as blood pressure can change rapidly and response to drug may be altered. Hypertension should be treated with titratable agents such as nicardipine or esmolol. Hypotension can be treated with Trendelenburg positioning, IV fluids, and pressors. Opioid or sedative drugs should be used with caution. Gastrointestinal and urinary regiments may be needed for constipation or retention. Patients may have increased sensitivity to several classes of medication, and these should be avoided or used with close monitoring (Table 12.8) [123].

Table 12.8 Autonomic instability is manifested in Guillain–Barré syndrome by exaggerated response to vasoactive medication

Drugs associated with increased autonomic instability in Guillain–Barré syndrome
Exaggerated hypotensive response
Phentolamine
Nitroglycerin
Edrophonium
Thiopental
Morphine sulfate
Furosemide
Exaggerated hypertensive response
Phenylephrine
Ephedrine
Dopamine
Isoproterenol
Tendency to provoke arrhythmia
Succinylcholine

These medications should be avoided or used with caution. Other short-acting agents should be used preferentially to treat symptomatic hemodynamic or rhythm instability. Adapted from Dalos [123].

Pain

Treatment of pain in Guillain–Barré syndrome often includes neuropathic and opioid medications. A small randomized controlled study of 18 patients admitted for ventilatory support for Guillain–Barré syndrome compared gabapentin to placebo and found that 15 mg/kg/day (divided in three dose) reduced pain score from 7.2 to 2.3, and also reduced requirements of rescue opioid analgesics [124]. Tegretol (300 mg for 3 days) in

a small study of 12 patients had similar benefits [125]. Oral or parenteral opioid analgesia is often necessary, with one study reporting 75% of patients receiving such treatment [44]. Again, vigilance regarding autonomic dysfunction is particularly important with opioid medications. Pain can be present in the chronic recovery phase of Guillain–Barré syndrome as well and neuropathic and longer acting opioids are often used.

Physical Therapy

Physical therapy in the acute phase of Guillain–Barré syndrome can help prevent complications related to prolonged immobilization, such as contractures. No controlled trials have looked at the benefits of specific types of physical therapy during the acute phase. In the recovery phase, fatigue may be very prominent (80%) despite relatively minimal neurologic residual deficits, which contributes to long-term reduction in functional ability in these patients. Amantadine has been studied as an agent to reduce fatigue, but no benefit was found [126]. A single case report has shown improved fatigue and functional outcome with fairly intense exercise programs (e.g., 30 min of stationary biking at 75% of maximal heart rate three times per week for 16 weeks) [127]. Another study examined effect of aerobic exercise in severely fatigued patients following Guillain–Barré syndrome (16 patients) or CIDP (four patients) and found improved fitness, fatigue, psychological wellness, and perceived functional status [128]. Thus, a regular, relatively intense exercise program should be instituted for patients recovering from Guillain–Barré syndrome to improve long-term function.

Conclusion

Guillain–Barré syndrome is the most common neuromuscular cause of acute weakness. The classic features are symmetrical weakness, areflexia, and CSF albuminocytological dissociation. Several variants are seen clinically. Given that the syndrome is immune-mediated, plasma exchange and IVIG along with supportive measures have greatly improved the treatment of Guillain–Barré syndrome. Further understanding of the pathogenesis of Guillain–Barré syndrome may offer new treatment strategies in patients who respond poorly with prolonged disability to current therapies.

Clinical Pearls

CSF pleocytosis suggests other infectious, inflammatory, or neoplastic processes instead of Guillain–Barré syndrome.

Preservation of reflexes in clinically weak limbs suggests a diagnosis other than Guillain–Barré syndrome.

Distal predominant "stocking-glove distribution" weakness and sensory loss in the absence of proximal weakness should raise concern for other causes of acute neuropathy, particularly toxic etiologies (e.g., metals, medication, solvent, etc.). This is because Guillain–Barré syndrome usually involves both roots and distal nerves, resulting in both proximal and distal weakness.

Severe, nonlocalized back pain may be a presenting feature of Guillain–Barré syndrome. Pain is often severe and is an under-recognized aspect of Guillain–Barré syndrome.

Children may present with a decrease in activity, irritability due to pain, and poor feeding. Areflexia in this setting may be an important clue.

Guillain–Barré syndrome remains a clinical diagnosis. Early normality of CSF and electrophysiological study is common and should not delay treatment if other clinical features are consistent with the diagnosis. Ancillary testing is not required prior to treatment.

Western blot serology testing in early stage of HIV seroconversion may be negative and PCR is needed for diagnosis. This is important when there are risk factors and a CSF pleocytosis suggesting HIV-related polyradiculoneuropathy.

As in other neuromuscular causes of respiratory weakness, desaturation and abnormal arterial blood gas are late signs of respiratory failure. Monitoring with clinical signs, forced vital capacity, maximal inspiratory, and expiratory pressures are more useful indices of respiratory distress.

Steroids are not useful and may be detrimental in Guillain–Barré syndrome.

If there is a plateau or deterioration of symptoms after initial immunotherapy, treatment-related fluctuation may be present and a repeat course of treatment may be needed. Greater than three recurrences or the development of new deficits may indicate that the presentation is in fact acute CIDP and steroids and continued scheduled treatments may be needed.

A moderately strenuous exercise program should be instituted in patients recovering from Guillain–Barré syndrome to maximize function and reduce post-Guillain–Barré syndrome fatigue.

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Spinal Cord Compression and Myelopathies

13

William F. Schmalstieg and Brian G. Weinshenker

Abstract

Patients with signs and symptoms of acute myelopathy require urgent neurologic evaluation focused upon the identification and management of treatable disorders. MRI of the spine is the imaging modality of choice to evaluate for a compressive lesion. When cord compression is present, surgical treatment is usually indicated. When compression is not detected, an analysis of precise lesion localization, nonneurological clinical features, MRI findings, and serologic studies narrow the differential diagnosis. The key diagnostic considerations include demyelinating, vascular, inflammatory, infectious, and paraneoplastic disorders. Empiric high-dose corticosteroid treatment is often indicated in noncompressive myelopathy; additional investigations are important to identify patients with relapsing or progressive disorders who may benefit from preventive therapies. Patients whose symptoms continue to progress after initial immunosuppressive treatment may benefit from plasmapheresis and occasionally from biopsy for definitive diagnosis.

Keywords

CNS • Demyelinating autoimmune disease • Magnetic resonance imaging • Myelitis • Spinal cord compression • Spinal cord diseases • Transverse

Acute myelopathies are potentially devastating conditions that may result in irreversible loss of mobility and control of bodily functions. Many etiologies of acute myelopathy are treatable, and rapid diagnosis and institution of appropriate treatment can prevent or reduce the extent of permanent damage to the spinal cord. Delays in the diagnosis and treatment of acute cord syndromes are frequent and may contribute to loss of neurologic function [1]. Furthermore, some inflammatory conditions that cause myelopathy may stabilize or remit but later relapse; patients with such conditions may benefit from maintenance prophylactic therapies, and therefore,

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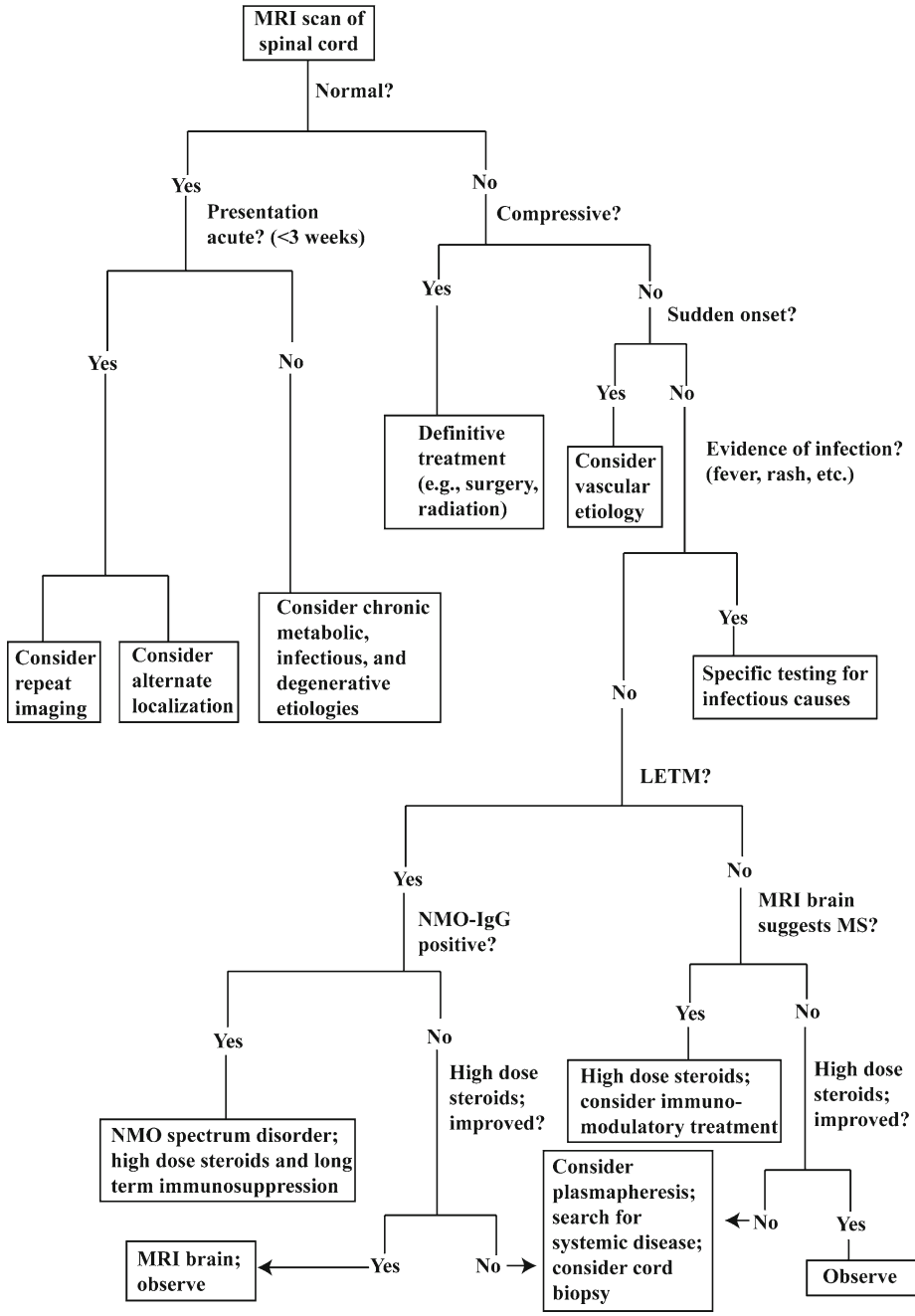

Fig. 13.1 Approach to diagnosis and management of acute and subacute myelopathies (*NMO* neuromyelitis optica; *LETM* longitudinally extensive transverse myelitis; *MS* multiple sclerosis)

consideration of the risk of relapse is important even when spontaneous or treatment-induced remission occurs.

This chapter considers the clinical presentation, evaluation, and management of acute and subacute spinal cord disorders and includes a diagnostic algorithm to distinguish compressive and noncompressive myelopathies and also to distinguish among the various noncompressive etiologies (Fig. 13.1). The key elements are high

index of suspicion and confirmation, primarily with neuroimaging, but occasionally supported by other laboratory studies. This chapter concludes with treatment recommendations.

Pathophysiology

A review of spinal anatomy informs a discussion of the pathophysiology and clinical presentation of acute disorders of the cord. The spinal cord extends between the medulla and the conus medullaris, the terminus of which ends opposite the L1 vertebral body. Much of the substance of the cord is composed of large myelinated tracts, the most clinically relevant of which include:

1. Lateral corticospinal tracts carrying ipsilateral motor fibers
2. Spinothalamic tracts carrying contralateral pain and temperature sensation
3. Dorsal columns carrying ipsilateral joint position and vibratory sensation

The arterial vascular supply of the spinal cord includes a single anterior spinal artery and two posterior spinal arteries, which originate from the vertebral arteries. The anterior spinal artery is also supplied by multiple segmental arteries arising from the thoracic and abdominal aorta. The anterior spinal artery supplies the lateral corticospinal and spinothalamic tracts, whereas the dorsal columns are supplied by the posterior spinal arteries. The venous drainage of the cord is through the epidural venous plexus.

The cord is surrounded by the meninges (pia, arachnoid, and dura mater), which are in turn encircled by the vertebrae. The vertebral bodies are anterior to the cord, the pedicles lateral, and the laminae and spinous processes posterior.

In compressive lesions, such as epidural abscess or metastatic disease, obstruction of the epidural venous plexus initiates spinal cord injury. Impairment of venous drainage causes vasogenic edema, which is in turn followed by an inflammatory cascade mediated, in part, by prostaglandins and other inflammatory cytokines. Simultaneously, the combination of external mechanical compression and internal swelling of the cord disrupts axonal conduction. Subsequent inflammation then leads to localized demyelination and frank ischemia of the cord [2].

Vascular occlusions or other vascular anomalies can cause acute cord injury. The portion of the cord supplied by the anterior spinal artery is particularly vulnerable. Restricted flow of the feeding vessels to this artery may produce watershed ischemia, particularly at the terminal regions supplied by the dominant radicular artery of Adamkiewicz as may occur during surgical cross-clamping of the aorta. Other potential causes of anterior spinal artery obstruction include aortic dissection, atherosclerosis, cardiac embolism, hypercoagulable states, and fibrocartilaginous embolism from intervertebral disk fragments. Another uncommon but important vascular anomaly associated with myelopathy is the dural arteriovenous fistula. In this condition, an abnormal connection of a dural artery to a vein results in venous hypertension, resulting in damage to the cord and leading to the telltale distension of the epidural venous plexus that is an important radiologic sign of this entity.

As elaborated in the section on differential diagnosis, a wide variety of demyelinating, inflammatory, and infectious conditions can produce intrinsic damage to the substance of the spinal cord. A detailed description of the underlying pathophysiology of each of these conditions is beyond the scope of this text, and in many of these conditions the pathogenesis is poorly understood.

One recent noteworthy discovery is that the NMO-IgG antibody, a clinically validated biomarker of neuromyelitis optica (NMO), may be responsible for an important portion of what had been previously regarded as "idiopathic transverse myelitis." NMO is an inflammatory demyelinating disease characterized by recurrent, severe attacks of optic neuritis and longitudinally extensive transverse myelitis [3]. The target of the NMO-IgG antibody is the aquaporin-4 (AQP4) water channel, which is highly expressed at the astrocytic end feet of the blood–brain barrier. Current evidence suggests that this antibody is pathogenic and not merely a marker of autoimmunity or disease severity. Brain MRI lesions in patients with NMO occur in regions known to

express high levels of AQP4 [4]. Additionally, transfer of pooled IgG antibodies from NMO-IgG positive patients to rats reproduces lesions similar to those seen in human NMO [5, 6]. Antibody- and complement-mediated cytotoxicity to astrocytes occurs in vitro in the presence of AQP4 autoantibodies and active complement and may account for the tissue damage seen in pathologic samples from patients with NMO [7]. Additional mechanisms that may contribute to injury caused by AQP4 specific autoantibodies include disruption of potassium and glutamate homeostasis due to the physical association of AQP4 with an inward rectifying potassium channel and the excitatory amino acid transporter EAAT2.

Differential Diagnosis

The differential diagnosis of acute myelopathy is extensive, including structural, vascular, demyelinating, infectious, inflammatory, neoplastic, and paraneoplastic conditions (Table 13.1).

Table 13.1 Etiologies of acute and subacute myelopathies

External compression
– Metastatic spinal cord compression
– Epidural abscess
– Spinal stenosis
– Disk herniation
– Spinal fracture
– Extramedullary hematopoiesis
– Epidural lipomatosis
– Atlantoaxial instability
Syrinx
Vascular
– Spinal cord infarct
– Intraspinal hematoma
– Dural arteriovenous fistula
Demyelinating
– Multiple sclerosis
– Neuromyelitis optica
– Idiopathic transverse myelitis
– Acute disseminated encephalomyelitis
Infectious-viruses
– Herpes viruses
– West Nile virus
– Dengue
– Picornaviruses (including enteroviruses, poliomyelitis)
– Rabies
Infectious-bacterial
– *Mycoplasma*
– *Chlamydia*
– Syphilis
– Tuberculosis
– Lyme disease (rare)
Infectious-parasitic
– Schistosomiasis
– Strongylosis
Inflammatory
– Sjögren syndrome
– Systemic lupus erythematosus
– Wegener granulomatosis
– Behçet disease
Sarcoidosis
Toxic/metabolic
– Nitrous oxide toxicity
– Copper deficiency
– Vitamin B12 deficiency (rare)
Iatrogenic
– Radiation myelitis
– Postvaccination myelitis
– Intrathecal chemotherapy
Neoplasia
– Intradural, extramedullary tumors (meningioma, neurofibroma)
– Intramedullary tumors (astrocytoma, ependymoma)
– Lymphomatoid granulomatosis
– Intravascular lymphoma
Paraneoplastic myelitis

Structural

External compression of the spinal cord is an important and treatable cause of acute myelopathy. Recognition of these conditions with MR imaging is usually considered straightforward. A typical example of cord compression in the setting of vertebral metastasis from a primary lung carcinoma is displayed in Fig. 13.2. It is essential to have a high index of suspicion for these disorders as few symptoms aside from pain may be present initially and neurologic deterioration can occur rapidly.

Spinal cord compression in the setting of congenital spinal canal stenosis and/or degenerative disk disease usually presents with subacute or chronic symptoms, although acute presentations can occur in the setting of trauma or acute disk

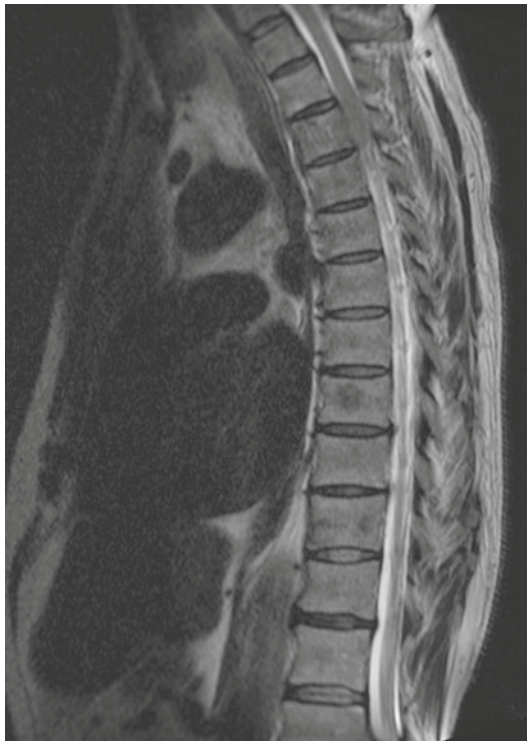

Fig. 13.2 Thoracic spinal cord compression caused by metastatic lung carcinoma, sagittal T2 MRI

herniation. Magnetic resonance imaging readily detects these abnormalities.

Occasionally, patients with myelopathy secondary to chronic stenosis, often due to a combination of congenital and acquired causes, will have dramatic longitudinally extensive cord signal abnormalities on MRI. These intrinsic cord abnormalities may cause the clinician to overlook an underlying spinal stenosis producing a subacute ischemic myelopathy due to compression, or the apparent cord compression may be attributed to cord edema from an intramedullary lesion rather than to the primary compressive process. Erroneous diagnoses of neuromyelitis optica, transverse myelitis, or spinal cord tumor may be made in these circumstances. However, patients with myelopathy secondary to stenosis usually develop symptoms over a period of several months, whereas transverse myelitis (either idiopathic or related to NMO) worsens to the point of maximal severity over days to weeks. In addition, gadolinium enhancement associated with stenosis tends to be quite focal and localized to the area of maximal compression, whereas enhancement in longitudinally extensive myelitis or tumor often extends over several vertebral segments (Fig. 13.3) [8].

Uncommon causes of extradural compression include extramedullary hematopoiesis, epidural lipomatosis, and atlantoaxial instability. Extramedullary hematopoiesis occurs in a number of hematologic disorders and in rare circumstances the epidural space may be involved. Reported causes include beta thalassemia, myelodysplastic syndromes, and polycythemia vera. Symptoms typically evolve over one to several months [9]. Epidural lipomatosis is a condition in which excess fat deposits form in the epidural space. Spinal cord compression can occur as a consequence, particularly in patients with preexisting spinal stenosis. Risk factors include endogenous or exogenous corticosteroid excess, obesity, and diabetes mellitus [10]. This condition often causes slowly progressive neurologic symptoms, but there are several reports of acute myelopathy related to epidural fat deposition [11]. Atlantoaxial instability is usually associated with an underlying condition and most commonly occurs in patients with rheumatoid arthritis or trisomy 21 [12, 13]. Patients with atlantoaxial dislocation may present with progressive myelopathy or acute spinal cord injury.

Spinal cord syrinx usually presents with a slowly progressive central cord syndrome. Characteristic findings include early occurrence of deep, poorly localized pain followed by loss of pain sensation at the level of the lesion, and progressive motor symptoms [14]. When a syrinx is present in the cervical cord, weakness appears initially in the upper limbs as the motor pathways to the arms are medial to those supplying the trunk and legs. Patients with this condition may present for acute evaluation when motor symptoms become bothersome or when painless injuries, especially burns, occur. Rarely, acute spinal cord damage due to syrinx occurs in the setting of trauma [15] or Valsalva maneuver [16].

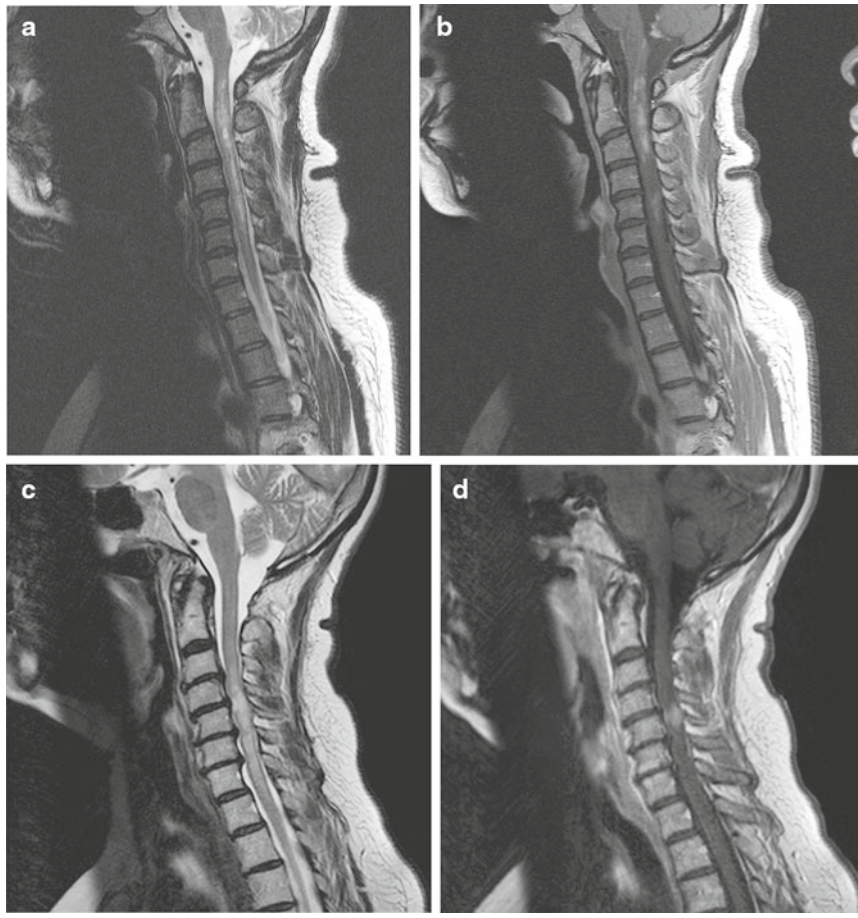

Fig. 13.3 Comparison of MRI imaging in transverse myelitis and compressive stenosis with longitudinally extensive intramedullary lesion; compressive stenosis is associated with a focal ring pattern of gadolinium enhancement at the point of maximal cord compression. (**a**) Transverse myelitis, sagittal T2 MRI. (**b**) Transverse myelitis, sagittal T1 MRI with gadolinium. (**c**). Compressive stenosis, sagittal T2 MRI. (**d**) Compressive stenosis, sagittal T1 MRI with gadolinium

Vascular

In the absence of a compressive lesion, the sudden onset of severe impairment of motor and spinothalamic sensory functions with relative preservation of dorsal column sensory modalities suggests a stroke in the distribution of the anterior spinal artery. This is a feared complication of surgical manipulation of the thoracic or abdominal aorta, and in that context is readily identified. However, cord infarction may occur spontaneously and occasionally without clearly identifiable risk factors that aid in the diagnosis.

MRI findings suggestive of anterior spinal cord infarction include central T2 hyperintensity with sparing of the posterior cord and swelling of the cord. Gadolinium enhancement is variable, and absence of enhancement in the setting of a sudden-onset myelopathy is more suggestive of infarct than an inflammatory process. Figures 13.4 and 13.5 display the evolution of a typical cord infarct.

Intraspinal hematomas are uncommon. These conditions can occur as a rare but serious consequence of lumbar puncture, especially in patients treated with anticoagulant drugs. A study of 342 patients who were anticoagulated with heparin after lumbar puncture demonstrated a 2% risk of spinal hematoma, whereas there were no hematomas in a matched cohort of patients who were not anticoagulated [17]. Patients with a recent history of spinal surgery, epidural anesthesia, or coagulopathy are

also at risk. Hemorrhage into the subarachnoid, subdural, or epidural spaces can occur, epidural hematoma being the most common [17]. Patients present with new, severe spinal pain and rapidly progressive neurologic deficits. These conditions can be readily identified with MR imaging.

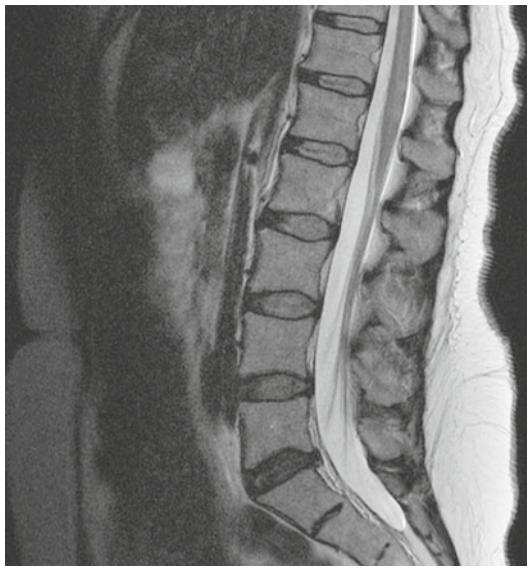

Fig. 13.4 Early cord infarct with patchy T2 signal change and swelling of the distal spinal cord, sagittal T2 MRI

A high index of suspicion for spinal arteriovenous fistula (AVF) is necessary as this is a treatable cause of progressive myelopathy. In the majority of cases, this condition produces a myelopathy that evolves over months. Some patients present with a stepwise course with repeated episodic deterioration related to upright posture or to minor exertion. Although this disorder is most common in men in the seventh decade of life, this potentially reversible process should be considered in all patients with an otherwise unexplained progressive or subacute myelopathy [18]. Abnormal high T2 signal in the cord extending into the conus and gadolinium enhancement are typical but nonspecific MRI findings of spinal dural AVF. The absence of any abnormal T2 signal is distinctly unusual in patients with dural AVF and suggests an alternate diagnosis. Presence of flow voids representing dilation of the epidural venous plexus is a more specific finding (Fig. 13.6), but may be seen in less than 50% of patients on standard MRI imaging. Prone-supine myelography is highly sensitive for detection of dilated epidural veins; the invasive nature of the procedure and substantial false positive rate limit the usefulness of myelography as a screening tool [18]. In patients with a stepwise or progressive myelopathy and radiologic findings suggestive of dural AV fistula, comprehensive

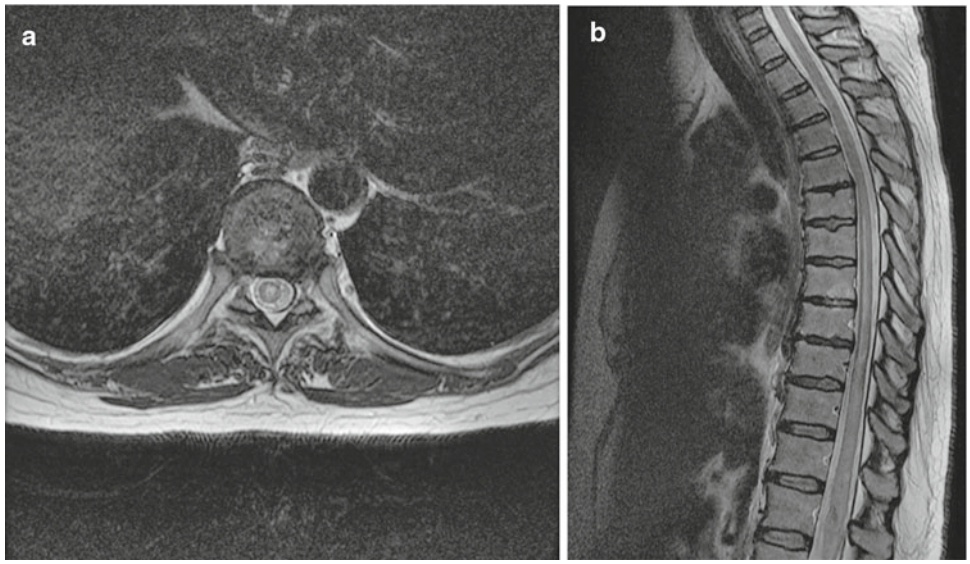

Fig. 13.5 Established cord infarct with central T2 hyperintensity. (**a**) Axial T2 MRI. (**b**) Sagittal T2 MRI

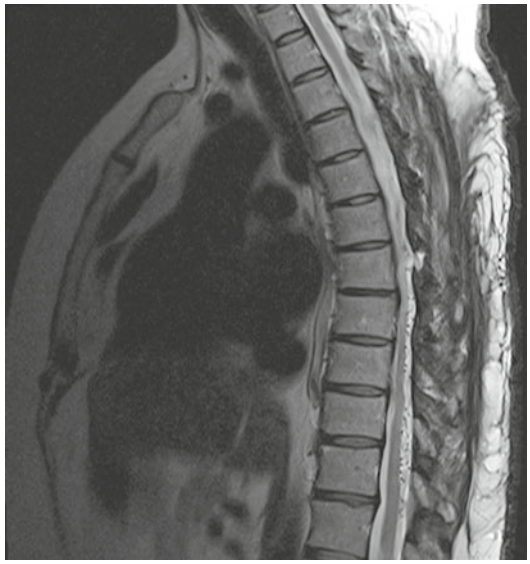

Fig. 13.6 Characteristic flow voids due to dilation of the epidural venous plexus in the setting of dural AVF, sagittal T2 MRI

spinal angiography may be warranted. Fistulae producing a progressive myelopathy may be found as high as the brainstem, and accordingly one needs to be determined to detect the abnormality in cases where the clinical and screening radiologic features strongly suggest that a fistula is present.

Demyelinating Disease

Demyelinating diseases account for a substantial percentage of acute myelopathies. Distinguishing patients who have or are at risk to develop MS from those with less common demyelinating disorders such as NMO, acute disseminated encephalomyelitis (ADEM), and idiopathic transverse myelitis is important for the prognosis of the patient and for selection of appropriate therapy to prevent recurrence.

In a patient presenting with a new, incomplete myelopathy the following features on spinal MRI should suggest the possibility of an MS-related lesion (Fig. 13.7):

1. Clearly circumscribed, focal T2 hyperintensity
2. Affects only part of the cord in axial cross section, usually, but not exclusively in the periphery of the spinal cord

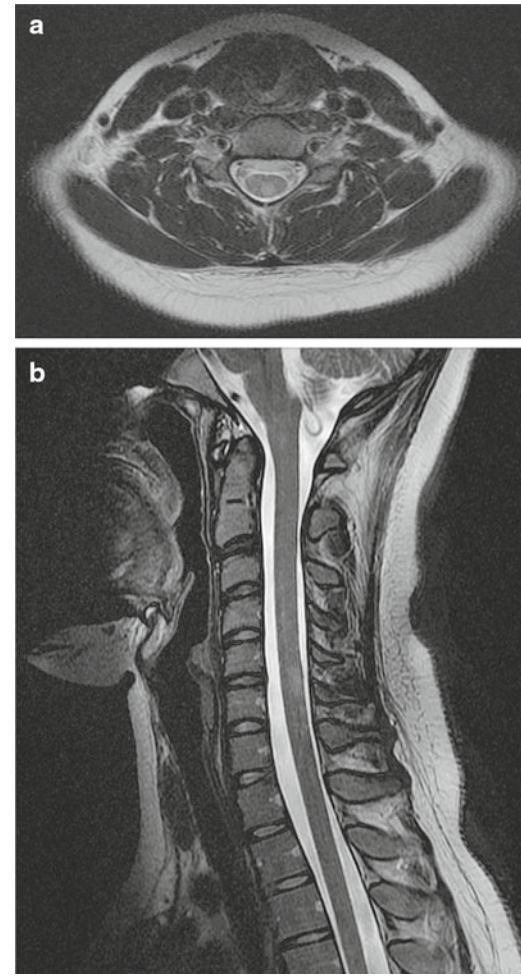

Fig. 13.7 Typical cord lesions caused by multiple sclerosis. (**a**) Axial T2 MRI. (**b**) Sagittal T2 MRI

3. Extends over less than two vertebral segments
4. Minimal or no cord swelling is present [19]

In patients with spinal lesions meeting these criteria, a careful history regarding any previous episodic neurologic symptoms may reveal a history of past MS exacerbations that assist with the diagnosis. MRI scan of the brain may detect typical brain lesions of multiple sclerosis (focal, T2 hyperintense lesions that are periventricular, juxtacortical, or located in the brainstem). However, nonspecific brain lesions are common due to definable (e.g., migraine) and nondefinable causes and therefore such lesions should not be assumed to be pathognomonic of MS. Additionally, brain

lesions are common in NMO and do not exclude that diagnosis [20].

Cerebrospinal fluid (CSF) examination is often performed in this setting, although this testing may be unnecessary in patients with a high pretest probability of having MS based on clinical and radiographic evidence. Detection of oligoclonal bands in the CSF, preferably by isoelectric focusing on agarose gels followed by immunodetection, is predictive of eventual development of MS independent of MRI findings [21]. Nevertheless, as oligoclonal bands are not present in all patients with MS and occur in other inflammatory, infectious, and neoplastic conditions, presence of oligoclonal bands should not be regarded as "diagnostic" of MS and the result of this study should not be used to guide treatment decisions in isolation. Other CSF findings that should suggest a diagnosis other than MS include a nucleated cell count greater than 50/μL and an excess of neutrophils.

Longitudinally extensive cord signal change extending over three or more vertebral segments is unusual in multiple sclerosis. Some authors argue for the existence of an opticospinal variant of MS in Asian patients that is distinct from NMO, and longitudinally extensive spinal cord lesions may occur in patients with that condition [22]. Nevertheless, the occurrence of longitudinally extensive transverse myelitis (LETM) in the setting of a previous history of one or more attacks of severe optic neuritis is highly suspicious for NMO and should prompt the clinician to obtain a serum NMO-IgG antibody. The sensitivity and specificity of this immunofluorescent antibody test in classic NMO are approximately 75% and >90%, respectively [3, 23].

Brain MRI is helpful in the evaluation of suspected NMO. Brain MRI lesions are common in NMO patients. In one series of 60 NMO patients, 60% had an abnormal brain MRI [20]. MRI lesions have been reported in NMO in regions of the brain known to express high levels of aquaporin-4, including the hypothalamus and periventricular regions [4]. However, brain lesions in NMO patients usually differ from lesions that are characteristic of MS.

CSF findings in NMO differ from those of MS; oligoclonal bands are infrequent in NMO and pleocytosis exceeding 50 WBC/μL and neutrophilic pleocytosis occur in approximately 25% of cases in the context of an acute attack [24]. Occasional patients have CSF NMO-IgG antibodies despite having negative results in serum [25].

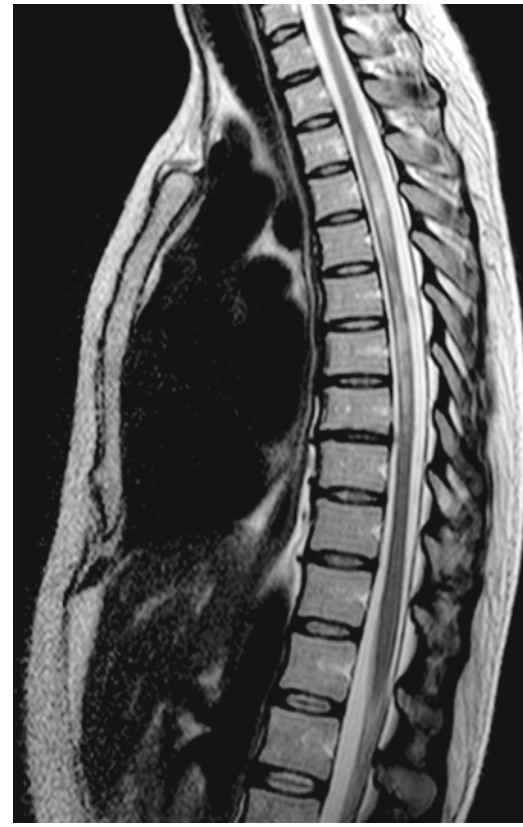

Fig. 13.8 Longitudinally extensive cord signal change caused by NMO, sagittal T2 MRI

Wingerchuk and colleagues have suggested the following diagnostic criteria for "definite NMO":

1. History of optic neuritis
2. History of acute myelitis
3. At least two of three supportive criteria
   (a) MRI demonstrating contiguous spinal cord lesion extending over ≥3 vertebral segments (Fig. 13.8)
   (b) Brain MRI at the onset of NMO symptoms that does not satisfy diagnostic criteria for MS
   (c) Seropositivity for NMO-IgG [23]

The absence of a history of optic neuritis does not exclude an NMO spectrum disorder. Some patients with an isolated LETM will subsequently develop classic findings of NMO. Others may have recurrent attacks of myelitis in the absence of optic neuritis, and may have a limited form of NMO. Presence of the NMO-IgG antibody in the setting of a single episode of LETM is strongly predictive of subsequent relapse; one series demonstrated a 55% risk of further episodes of myelitis and/or optic neuritis within one year in patients with a LETM [26].

Acute myelopathy may occur in the setting of ADEM, a multifocal demyelinating disorder of the CNS that typically occurs after an infectious syndrome or recent vaccination; it is more common in children. In the classic presentation, MRI demonstrates multifocal gadolinium-enhancing CNS lesions. The most specific criterion that distinguishes ADEM from MS, and is required for the diagnosis, is encephalitis [27].

Patients with a symmetric, severe acute myelopathy ("complete transverse myelitis") and/or isolated LETM with negative NMO-IgG may have an isolated inflammatory demyelinating transverse myelitis (i.e., idiopathic transverse myelitis) or another infectious, inflammatory, or neoplastic condition. As discussed below, serum and CSF testing may reveal evidence of a parainfectious cause in these patients; when such testing is unrevealing, clinical and radiographic follow-up is important. In patients in this group who display ongoing clinical deterioration beyond 3 weeks or have worsening findings on MRI, biopsy of the spinal cord should be considered to exclude tumor or another treatable inflammatory disorder, such as neurosarcoidosis.

Infectious

In addition to compression by an extrinsic infectious lesion such as an epidural abscess, some pathogens can produce acute or subacute myelopathies by direct infection of the cord or by inducing a parainfectious, presumably autoimmune process.

Clinical features that should prompt an increased level of suspicion for an infectious process include current or recent presence of fever, meningismus, rash, symptoms of systemic illness, recent travel, or immunosuppression. Although nonspecific, CSF pleocytosis (particularly if greater than 50 WBCs/μL) suggests this possibility. However, patients with parainfectious myelopathy often do not recall or have symptoms of a recent illness. In a review of 23 patients with parainfectious myelopathy confirmed by serological or CSF studies, only nine (39%) recalled symptoms consistent with an infectious process in the previous month [28].

Viruses are the most common cause of parainfectious myelopathy [28]. CSF PCR testing for herpes viruses (herpes simplex virus 1 and 2, Epstein–Barr virus, varicella zoster virus, cytomegalovirus, human herpesvirus-6) is appropriate in an unexplained myelopathy as these viruses are the most commonly identified causes of parainfectious myelopathy and may be treatable with specific antiviral therapies [28]. A multitude of other viruses have been implicated as causes of infectious or parainfectious myelitis, including adenoviruses, coxsackie B virus, enteroviruses, measles [28], and dengue [29].

Certain viral infections characteristically produce an acute flaccid paralysis with sparing of sensory function when involving the central nervous system. Poliomyelitis is the classic example of such a condition. This disorder is now extraordinarily rare in developed countries, although importation of this disease from endemic regions [30] and limited person to person spread in an undervaccinated community have been reported in recent years [31]. Similar clinical presentations have been associated with epidemics of enterovirus 70 (acute hemorrhagic conjunctivitis) and enterovirus 71 (hand, foot, and mouth disease) [32], as well as West Nile virus [33]. In a minority of cases, rabies encephalomyelitis can also present as an ascending flaccid paralysis with spinal cord signal change [34].

Parainfectious myelitis may occur in association with recent bacterial infections, often with *Chlamydia* and *Mycoplasma* species [28]. Myelitis

can occur in *Mycobacterium tuberculosis* infection either due to direct involvement of the cord or on a compressive basis in the setting of vertebral involvement (Pott disease). Bacterial myelitis can also occur with *Treponema pallidum* (syphilis) [35] or *Borrelia burgdorferi* (Lyme disease) infections [36]; both of these presentations are uncommon.

Fungal and parasitic infections are rare causes of acute myelitis, but should be considered in patients at risk due to immunosuppression and/or travel exposures. Infections associated with acute myelopathies include schistosomiasis [37], strongylosis, candidiasis [28], and blastomycosis [38].

Inflammatory

In addition to inflammatory demyelinating diseases, other systemic inflammatory disorders can produce acute or subacute myelopathies. Myelopathy can occur as a complication of Sjögren syndrome or systemic lupus erythematosus. However, antibodies associated with these syndromes (e.g., ANA, SS-A) are encountered in patients with NMO and may occur in other inflammatory demyelinating diseases. A serological survey of 153 patients with NMO spectrum disorders found positive ANA and SS-A antibodies in 44% and 16%, respectively [39]. Accordingly, diagnoses of lupus or Sjögren syndrome should not be made on the basis of antibody findings alone in cases of acute myelopathy unless specific diagnostic criteria for these diseases are met.

Behçet disease is a chronic, relapsing inflammatory disorder characterized by recurrent oral aphthous ulcers and other systemic manifestations including recurrent genital ulcerations, eye, and skin lesions [40]. Spinal cord and other nervous system involvement occurs in a minority of patients with this condition, either due to direct formation of lesions in the CNS or secondary to infarct from involvement of major vascular structures [41]. Presence of a positive pathergy test (development of a nodule ≥2 mm in diameter 24–48 h after subcutaneous insertion of a sterile needle) is accepted as a supportive criterion for diagnosis of this disease, but this test is insensitive and does not establish a diagnosis in isolation [40]. There are no other laboratory or imaging findings that are unique to this condition, and accordingly the diagnosis requires presence of other characteristic systemic features.

Sarcoidosis is a nonnecrotizing granulomatous inflammatory process that can involve multiple organ systems. Neurological involvement occurs in approximately 5% of cases, and in those cases, neurologic symptoms are the initial manifestation in about half [42]. In the absence of systemic disease, the diagnosis of neurosarcoidosis is often difficult. Spinal imaging findings that may suggest this process include a nodular enhancing pattern in the parenchyma, meningeal enhancement, and nerve root enhancement. Oligoclonal bands in the CSF have been reported in 27–51% of cases; the presence of oligoclonal bands should not automatically lead to a diagnosis of MS [43, 44]. Although neither sensitive nor specific, an elevated serum ACE level may suggest sarcoidosis as well. In patients with imaging findings suspicious for sarcoid and those with an otherwise unexplained myelopathy, it is helpful to search for evidence of systemic sarcoid in a lesion that could be biopsied (e.g., an enlarged lymph node). CT imaging of the chest may demonstrate evidence of hilar lymphadenopathy. Blind conjunctival biopsy occasionally demonstrates characteristic noncaseating granulomatous inflammation. In cases of isolated CNS involvement, such studies will be unrevealing and empiric corticosteroid treatment for both therapeutic and diagnostic purposes is often the best approach; dramatic and sustained improvement in the face of a syndrome suggestive of sarcoidosis is often the basis of a tentative but acceptable diagnosis.

Toxic/Metabolic

Metabolic disorders affecting the cord usually produce a chronic myelopathy, although many patients will not complain of symptoms until a certain level of impairment develops. In most, careful history reveals that the symptoms of

myelopathy are long-standing. Nevertheless, given that the diagnosis and treatment of these disorders is associated with minimal risk, obtaining limited metabolic studies such as serum vitamin B12, methylmalonic acid, and copper levels is appropriate in the setting of unexplained subacute or chronic myelopathies.

Acute myelopathies have occurred secondary to toxic exposures from consumption of toxic dietary staples (e.g., cassava, *Lathyrus sativus*) or recreational substance abuse (e.g., tricresyl phosphate toxicity from consumption of adulterated "Jamaican ginger" extract); many of these conditions are of limited historical or geographic relevance [45]. An exception is myelopathy secondary to nitrous oxide exposure. Nitrous oxide can produce myelopathy via irreversible oxidation of cobalamin, resulting in secondary vitamin B12 deficiency [45]. Individuals with preexisting subclinical vitamin B12 deficiency are particularly vulnerable. This condition continues to occur secondary to recreational abuse [46] and rarely in patients receiving nitrous oxide anesthesia [47] or dental professionals working in poorly ventilated offices [46]. In recreational users, specific questioning about use of nitrous oxide is important as users may be reluctant to admit this habit and unaware of its toxic potential.

Iatrogenic

Patients who have undergone radiation treatment for cancer can develop radiation myelitis when the spinal cord is included in the radiation field. This condition can present acutely during radiation treatment or in a delayed fashion. In a patient with a history of cancer, it is essential to exclude direct metastatic involvement of the cord prior to attributing any myelopathy to radiation effect.

Autoimmune myelitis may occur after vaccinations. Classic descriptions of postvaccination encephalomyelitis occurred in individuals who received obsolete forms of rabies vaccination, but postvaccination myelitis has been reported after a host of other common vaccinations including influenza, pertussis, diphtheria-tetanus, MMR, and hepatitis B [48]. However, the onset of myelopathy after vaccination may be purely coincidental and recent vaccination should not deter investigations to uncover other treatable causes.

Subacute myelopathy also may result from toxic effects of intrathecal chemotherapy with several agents including methotrexate, doxorubicin, vincristine, and cytarabine [45].

Neoplastic and Paraneoplastic

Intramedullary neoplasms, such as astrocytomas and ependymomas, and extramedullary, intradural tumors, such as meningiomas and neurofibromas, may become symptomatic with a subacute time course mimicking extradural tumors or transverse myelitis. These tumors are easily visualized on MRI, although they may sometimes be confused with inflammatory lesions. Biopsy is usually required to confirm the diagnosis.

Lymphoproliferative malignancies, such as lymphomatoid granulomatosis and intravascular lymphoma, can involve the spinal cord and evolve with a subacute time course. Confident diagnosis requires biopsy of the CNS or other involved site, although in the case of lymphomatoid granulomatosis the presence of oligoclonal bands and positive CSF PCR for Epstein-Barr virus increases the index of suspicion.

Myelitis may occur as a paraneoplastic disease. The index of suspicion for a paraneoplastic process should be increased in patients with a known history of cancer and in smokers. A serum evaluation for paraneoplastic autoantibodies should be considered in these circumstances. Certain imaging patterns may also be suspicious for a paraneoplastic etiology; we have encountered a number of patients with hyperintense T2 lesions that appear confined within individual spinal tracts in this circumstance, often symmetrically on both sides of the cord (Fig. 13.9) [49]. Paraneoplastic syndromes may produce multifocal nervous system involvement mimicking other disorders such as NMO. In particular, collapsin response-mediator protein-5 (CRMP-5) IgG antibodies can cause autoimmune myelitis and optic neuritis [50, 51].

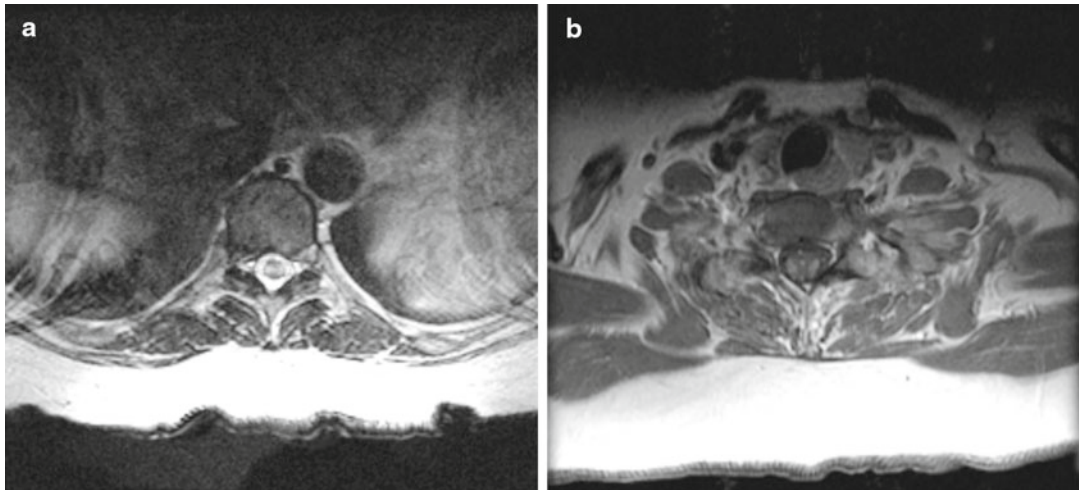

Fig. 13.9 Signal change in the central cord and lateral columns caused by paraneoplastic myelitis in the setting of renal cell carcinoma. (**a**) Axial T2 MRI. (**b**) Axial T1 MRI with gadolinium

Alternate Localizations

When there is no spinal cord abnormality on neuroimaging in the context of an apparent acute myelopathy, the responsible lesion may be elsewhere in the nervous system. The primary item on the differential diagnosis in patients with bilateral motor and sensory symptoms is an acute neuropathy such as Guillain–Barré syndrome. In addition to ascending weakness, findings favoring this diagnosis include areflexia, absence of a defined sensory level, and elevated protein concentration in the CSF with a normal cell count. In patients with pure motor symptoms, myopathies and occasionally neuromuscular junction disorders can be mistaken for spinal cord disease. Parafalcine space-occupying lesions (e.g., meningioma) and bilateral anterior cerebral artery distribution infarcts occasionally present with bilateral lower limb weakness mimicking myelopathy as well.

However, the absence of an MRI abnormality should not automatically lead to the conclusion that the problem does not localize to the spinal cord. Subtle imaging abnormalities such as swelling of the cord in the absence of signal change, as occasionally seen in early cord infarct, or symptomatic epidural lipomatosis may be missed on initial review. The possibility of an "acute" presentation of a chronic metabolic, degenerative, or infectious disorder (e.g., AIDS myelopathy, tropical spastic paraparesis due to HTLV-I) should also be considered, although these conditions rarely evolve during short-term neurologic follow-up. Occasionally, patients with chronic myelopathies do not seek medical attention despite long-standing symptoms until they become associated with functional impairment.

Epidemiology

Metastatic spinal cord compression is a common complication of advanced cancer, occurring in 2.5–6% of individuals with systemic malignancy ascertained in population-based studies [52, 53]. In approximately 20% of cases, cord compression is the presenting manifestation of cancer [54]. Metastases attributable to a specific cancer generally parallel the relative frequency of that cancer, with approximately half of cases attributable to carcinomas of the breast, prostate, and lung [52]. However, certain malignancies including renal cell carcinoma [52], multiple myeloma, and lymphoma [54] are disproportionately more likely to result in cord compression, whereas gastrointestinal cancers, including colorectal and pancreatic carcinoma, are disproportionately less likely to do so [53].

As MS is a relatively common disorder (prevalence estimated at 0.9 cases per 1,000 in the United States population [55]) and the majority of patients have imaging evidence of spinal cord involvement even at the time of diagnosis [56], MS is responsible for a substantial proportion of acute myelopathies. MS plaques in the cord often result in minimal symptoms, and are asymptomatic in up to two-thirds of cases [57]. Milder myelopathic presentations with asymmetric motor and sensory involvement (i.e., "partial transverse myelitis") are the most common myelopathies that are manifestations of inaugural or established MS [58].

Other individual causes of nontraumatic, acute myelopathy are uncommon. For instance, retrospective studies suggest that the incidence of acute transverse myelitis in patients without a previous history of neurologic disease ranges from 1.3 to 4.6 cases per million per year [59, 60]. Similarly, epidural abscess was diagnosed at a rate of only 2 of 10,000 hospital admissions per year at an urban referral center [61]. Collectively, however, these less common entities constitute an important group of disorders that may need very specific treatment.

The etiology of new-onset, noncompressive myelopathy is often unclear at the time of presentation. A recent French series reported that the etiology of acute myelopathy could not be determined in 101 of 170 patients at onset. Fifty-four percent of these patients were subsequently diagnosed with either multiple sclerosis (45 patients), neuromyelitis optica (5 patients), or a connective tissue disease (5 patients). Many patients with each of these disorders would likely benefit from maintenance therapies to prevent relapse. This result highlights the importance of diagnostic testing in cases of acute noncompressive myelopathy, as many patients with this type of presentation have treatable disorders with potential to result in serious future morbidity.

Demographics and Other Risk Factors

Age, gender, ethnicity, and race may suggest that a particular cause of acute myelopathy is more or less likely. Demographic features associated with selected causes of acute myelopathy are presented in Table 13.2 [18, 62–65]. Most causes of acute myelopathy are not restricted by demography, and age, gender, and ethnicity do not exclude any etiology from consideration in an individual patient.

Recognition of risk factors related to habits or other medical history is equally important. Risk factors associated with particular causes of myelopathy are listed in Table 13.3.

Table 13.2 Demographic factors associated with specific causes of myelopathy

Metastatic spinal cord compression: prior history of malignancy, elderly patients and children; uncommon in young adults
Multiple sclerosis: median age of onset in third decade of life; more common in females
Neuromyelitis optica: relapsing form more common in women; non-Caucasians overrepresented in US patients relative to MS
Spinal cord infarct: increased risk with age; male sex
Dural arteriovenous fistula: most common in seventh decade of life; male predominance
Systemic lupus erythematosus/Sjögren syndrome: female predominance
Behçet disease: most common in patients of Middle Eastern and Far Eastern origin; more common in males of Middle Eastern origin and more severe in males
Sarcoidosis: more common in women; three–fourfold greater risk in African Americans compared to Caucasians

Table 13.3 Risk factors associated with specific causes of myelopathy

Cigarette smoking: metastatic spinal cord compression, paraneoplastic myelopathy, cord infarction
Injection drug use: epidural abscess
Nitrous oxide abuse: myelopathy due to induced vitamin B12 deficiency
Immunosuppression: epidural abscess, other infectious myelopathies
History of cancer: metastatic spinal cord compression, toxic myelopathy with history of intrathecal chemotherapy, radiation myelitis with history of radiotherapy
Obesity: epidural lipomatosis
Corticosteroid excess: epidural lipomatosis
GI malabsorption or surgery: myelopathy due to nutritional deficiency, including B12 and copper deficiency
Excess zinc ingestion: myelopathy due to copper deficiency

Clinical Features

Syndromes

Presentations of spinal cord disease are often described in terms of clinical syndromes. Spinal cord syndromes associated with specific etiologies are listed in Table 13.4. Although the type of clinical presentation seen may help to narrow the differential diagnosis, none of these syndromes are pathognomonic for any particular condition. Accordingly, recognition of other characteristic clinical features, imaging findings, and the results of other diagnostic studies are necessary for accurate diagnosis.

Table 13.4 Etiologies of spinal cord syndromes

Brown-Séquard syndrome
Multiple sclerosis
Penetrating trauma
Metastatic cord compression
Epidural abscess
Parainfectious myelopathy
Anterior cord syndrome
Anterior spinal artery infarct
Disk herniation
Metastatic cord compression
Epidural abscess
Radiation myelitis
Trauma
Central cord syndrome
Syringomyelia
Intrinsic spinal cord tumor
Neuromyelitis optica
Transverse myelitis
Trauma
Posterior cord syndrome
Multiple sclerosis
Posterior spinal artery infarct
Tertiary syphilis
Subacute combined degeneration due to B12 or copper deficiency
Conus medullaris syndrome
Disk herniation
Metastatic cord compression
Intrinsic spinal cord tumor
Trauma
Dural arteriovenous fistula
Demyelinating disease
Complete cord syndrome
Idiopathic transverse myelitis
Trauma
Metastatic cord compression
Epidural abscess
Hemorrhage
Ischemia

Brown-Séquard Syndrome

"Complete" Brown-Séquard syndrome refers to the clinical presentation seen with hemisection of the spinal cord. An affected patient has loss of motor function and dorsal column sensory modalities on the side of the lesion, with pain and temperature loss below the level of the lesion on the opposite side of the body due to disruption of the spinothalamic tract. The complete presentation is unusual; a "partial" Brown-Séquard syndrome with preservation of dorsal column sensory function is more common. This type of asymmetric presentation is often seen in demyelinating diseases, particularly MS, but can also occur in the early stages of a compressive lesion.

Anterior Cord Syndrome

In this presentation, the corticospinal and spinothalamic tracts are injured bilaterally with preservation of dorsal column sensory functions. This syndrome is seen with infarction of the anterior spinal artery, but can also occur with compressive lesions.

Central Cord Syndrome

The characteristic evolution of a central cord syndrome in the setting of a syrinx was described earlier. Common features include deep, uncomfortable pain, loss of pain and temperature sensation at the level of the lesion due to disruption of the crossing fibers of the spinothalamic tracts, and impairment of motor function in the upper limbs prior to the lower limbs and trunk. In addition to syrinx and cord tumor, the features of central cord syndrome can occur with inflammatory demyelinating diseases, particularly neuromyelitis optica.

Posterior Cord Syndrome

Isolated involvement of the dorsal columns is most commonly seen in the setting of a chronic myelopathy; tabes dorsalis in the setting of tertiary syphilis is a classic example. This syndrome

occasionally occurs due to infarction of the posterior spinal artery.

Conus Medullaris Syndrome

Myelopathy confined to the terminal portion of the spinal cord results in flaccid paralysis of the bladder and anal sphincters. The presentation may occur as a component of a more extensive cord lesion involving the conus or be quite isolated. There are multiple causes including compression, dural arteriovenous fistula, neoplasm, and demyelination. One needs to distinguish this presentation from a cauda equina syndrome. Compression or inflammation of the cauda equina produces lower motor neuron findings including weakness and reflex loss in the lower limbs corresponding to the involved nerve roots as well as sensory changes in the dermatomes innervated by involved sensory roots. Pain is usual in cauda equina syndrome; bowel and bladder involvement is variable depending on the levels involved.

Complete Cord Syndrome

The clinical picture of complete transection of the spinal cord at the level of the lesion (absence of all sensory modalities and motor function below the lesion) is described as the complete cord syndrome. This type of presentation occurs with severe idiopathic transverse myelitis and is also a common presentation of an extradural compressive lesion producing severe cord compression.

Symptoms

Although many symptoms of acute cord injury are nonspecific, certain symptoms are characteristic and suggestive of particular conditions.

Pain is not unique to cord compression, but is an important "red flag." In the majority of cases of metastatic SCC, pain precedes the onset of other neurologic symptoms. Pain in the thoracic region is particularly concerning, not only because the majority of metastatic cord compressions occur in this region [66], but also because "benign" musculoskeletal and radicular causes of pain in the thoracic spine are far less common than in the neck or low back. Pain that worsens at night or with recumbent position is also suggestive of cord compression.

A history of prior neurological symptoms is often informative in the diagnosis of inflammatory demyelinating diseases. A history of previous episodic visual, motor, urinary, or sensory disturbances lasting greater than 24 h may suggest previously unrecognized MS exacerbations. A history of clear worsening of neurologic symptoms in response to heat or a reproducible "shock-like" sensation traveling down the spine with forward flexion of the neck (Lhermitte sign) is quite suggestive of demyelination. Paroxysmal tonic spasms (brief, involuntary muscle contractions typically lasting from 15 to 60 s at a time) are a less common but highly specific indicator of an inflammatory demyelinating disease. A history of episodes of intractable vomiting or hiccoughs is now recognized as a common harbinger of NMO spectrum disorders [67, 68].

Time Course

Myelopathies can develop suddenly, acutely (<24 h to 3 weeks), subacutely (over weeks to months), or insidiously. Apoplectic onset of symptoms often suggests a vascular etiology such as an ischemic cord infarct or occasionally a hemorrhage. Compressive lesions can also present abruptly, as in the case of an acute disk herniation or a pathologic fracture in the setting of malignancy. Inflammatory disorders usually do not present instantaneously, but patients may awaken with new symptoms and thereby confound the determination of the mode of onset.

Many etiologies of myelopathy, such as demyelinating diseases, other inflammatory disorders, and cord compression, reach maximal severity over days to a few weeks. Other conditions that can present with a similar time course include parainfectious myelopathy, radiation myelitis, and paraneoplastic myelitis. Disorders that evolve over weeks or longer include spinal stenosis, dural arteriovenous fistula, chronic infections (e.g., HIV myelopathy, HTLV-I, tertiary syphilis), metabolic disorders, and intradural and intramedullary tumors.

Diagnosis

Neuroimaging, and to a lesser extent, other diagnostic studies are essential for accurate diagnosis of acute and subacute myelopathies given the lack of specificity of clinical and demographic features. A stepwise approach to diagnostic testing is discussed; specific features suggestive of particular disorders were presented earlier.

Spine MRI

MRI scan of the spine is the key diagnostic procedure in the assessment of acute cord lesions. The superiority of MR imaging in visualizing soft tissue makes MRI the procedure of choice in assessing inflammatory, vascular, infectious, and metabolic myelopathies. MRI has also supplanted CT myelography as the preferred procedure in cases of suspected cord compression. In metastatic SCC, MRI is equally sensitive and more specific than CT myelography [69, 70]. Additionally, myelography may result in neurologic deterioration in patients with severe compression who have complete block of the flow of myelographic dye.

Patients with cord compression may experience significant neurologic deterioration over a period of a few hours. When suspected, MRI imaging should be obtained on an emergent basis and not delayed. If a compressive lesion is identified, definitive treatment with surgery or radiotherapy is indicated. Although additional testing to identify the underlying condition causing compression is important, treatment is urgently needed and should not be delayed to obtain additional testing; however, radiotherapy may not be provided until a definitive diagnosis of cancer is obtained at the time of surgery in patients without an established history of cancer.

When abnormal signal is apparent within the substance of the cord, a review of the past history, clinical presentation, and imaging findings may suggest a particular diagnosis. However, in many cases further studies are necessary.

CSF Examination

A CSF examination is often the next step in the evaluation of a noncompressive myelopathy. CSF examination is usually not helpful in diagnosing the cause of spinal cord compression and may result in neurologic deterioration in patients with severe cord compression. Routine CSF studies should include cell count with differential, glucose and protein concentration, oligoclonal banding, and cytologic examination; it is often helpful to retain spinal fluid to allow for additional testing informed by the results of the initial screening tests.

Brain MRI

In cases of acute, noncompressive myelopathy, brain MRI imaging is useful to detect characteristic features of demyelinating disease. In the setting of an asymmetric partial transverse myelitis, presence of brain lesions consistent with MS strongly suggests that the presentation is due to inflammatory demyelinating disease. In patients with a clinically isolated demyelinating syndrome, the finding of typical MS lesions on brain MRI predicts an approximately 90% chance of developing clinically definite MS in the future [71]. However, a normal brain MRI scan does not exclude the diagnosis of a demyelinating disease. It is also important to distinguish the typical periventricular, juxtacortical, and brainstem lesions of MS from nonspecific T2 signal abnormalities in the deep subcortical white matter, which do not have the same diagnostic implications when seen in isolation.

Blood/Serology

Serum NMO-IgG antibody serology should be obtained in patients with unexplained longitudinally extensive (≥3 vertebral segments in length) signal abnormality regardless of whether or not a patient has a past history of optic neuritis. In contrast, patients with a history of optic neuritis and partial transverse myelitis *without* longitudinally

extensive cord signal change are *unlikely* to have NMO; MS is a more likely diagnosis in this context.

In patients with isolated myelitis and otherwise normal CNS imaging, viral serologies may yield evidence supporting a role of common pathogens associated with parainfectious myelopathy. CSF PCR studies may be a more reliable marker of recent infection. Detecting evidence of recent infection with herpes viruses is important as patients may respond to specific antiviral therapy with acyclovir and related compounds. Even in cases where a positive result does not alter the treatment strategy, finding evidence of a recent infection may limit the need for additional diagnostic testing.

When an underlying systemic inflammatory disease is suspected, obtaining an antinuclear antibody (ANA), anti-double stranded DNA antibodies, antibodies to extractable nuclear antigens (e.g., SS-A), and antineutrophil cytoplasmic antibodies (p-ANCA and c-ANCA) may be useful to screen for systemic inflammatory and vasculitic disorders. However, when clinical and radiographic findings strongly suggest an inflammatory demyelinating disease, a "positive" serologic result, such as a positive ANA, is unlikely to indicate an alternate diagnosis, especially considering the nonspecificity of this antibody. A "panel" of serologic markers of autoimmunity to screen for "mimics" of multiple sclerosis is not helpful and may be misleading given the high frequency of false positive results when used as a screening test.

Blood/Other

Additional laboratory tests may be valuable in diagnosing the cause of a compressive myelopathy, although usually not essential to emergent management. In cases where cord compression is the initial manifestation of an occult cancer, prostate-specific antigen testing and monoclonal protein studies of the serum and urine (often positive in multiple myeloma and other plasma cell dyscrasias) may suggest an underlying malignancy. When epidural abscess is considered, blood cultures should be obtained from two separate sites, ideally prior to the institution of empiric antibiotic therapy. The yield of blood cultures in epidural abscess is approximately 60%, with the most common organism being *Staphylococcus aureus* [72].

Other Imaging Studies

In patients who are unable to undergo MRI because of implanted MRI-incompatible medical devices, presence of magnetic foreign bodies, or body habitus, CT myelography is an alternative imaging modality to exclude compression.

CT imaging of the chest, abdomen, and pelvis may reveal an underlying cancer in cases of occult malignancy presenting with cord compression. In noncompressive myelopathies that are atypical for demyelinating disease, CT imaging may also be useful to screen for lymphadenopathy suggestive of sarcoidosis or lymphoma.

Gallium-67 scintigraphy occasionally reveals evidence suggestive of sarcoidosis when routine CT imaging is negative. Positron emission tomography (PET) scan can detect an otherwise occult malignancy in cases of cord compression or finding of a positive paraneoplastic autoantibody.

Treatment

Compressive

Despite availability of MRI imaging, delays in the treatment of metastatic cord compression remain common. In one series of 301 patients, only 33% were ambulatory at the time of treatment, unchanged from the era prior to MRI imaging. Most had experienced deterioration in motor function *after* initial presentation to a medical practitioner before definitive treatment was instituted [1]. Patients who are nonambulatory often remain so; nearly 40% of nonambulant patients remain unable to walk after treatment [73]. In contrast, 80–100% of spinal cord compression patients who are ambulatory at the time of treatment initiation remain ambulatory [52, 74–76]. Accordingly, rapid identification of cord compression and early definitive treatment are essential

for optimal outcomes. Corticosteroids and surgical decompression were proven effective for treatment of metastatic spinal cord compression in controlled clinical trials, and the standard of care also includes radiotherapy.

A single placebo-controlled trial addressed the use of corticosteroids as an adjunct to radiation therapy in metastatic cord compression. The treatment group received 96 mg of intravenous (IV) dexamethasone at presentation and then 24 mg of oral dexamethasone four times daily for 3 days followed by taper. At the conclusion of treatment, 81% of the dexamethasone-treated group versus 59% of the placebo-treated group were ambulatory; at 6 months, 63% of patients in the treatment group versus 33% of the placebo-treated group were ambulatory [77]. Two small trials comparing high-dose dexamethasone (96–100 mg initial IV dose) to lower doses (10–16 mg) did not demonstrate a statistically significant difference in outcome between the two doses [78, 79]. Nevertheless, we recommend that patients with limb weakness in the setting of metastatic cord compression receive an initial dose of 100 mg of dexamethasone IV followed by 16 mg daily, subsequently tapered over approximately 2 weeks.

Patchell and colleagues reported a randomized but nonblinded trial of direct decompressive surgery for metastatic cord compression followed by radiotherapy versus radiotherapy alone. Patients in the surgery group were more likely to remain ambulatory (84% versus 57%, p 0.001) and for a longer interval (median 122 days versus 13 days, p 0.003) compared to the radiotherapy only group. In patients unable to walk prior to treatment, a higher percentage of surgically treated patients regained that capacity (62% versus 19%, p 0.01). Patients with lymphoma were excluded as this tumor is considered highly radiosensitive, as were those who had been nonambulatory for greater than 48 h. On the basis of this trial, surgery is recommended for symptomatic patients with spinal cord compression who would be able to tolerate it [73].

In patients who are poor surgical candidates due to baseline functional status or short life expectancy, radiotherapy alone is also beneficial in relieving pain and preserving ambulatory capacity [75]. No specific radiotherapy regimen has been proven superior. In the United States, patients often receive 30 Gy to the involved area in equal doses over 10 days. Some authors have advocated lower doses, with doses as low as 8 Gy in a single fraction appearing beneficial in a randomized trial [80].

The treatment of other causes of spinal cord compression is usually surgical. Although no controlled trials have addressed the issue of surgical versus medical management of epidural abscess, surgical decompression followed by antibiotic treatment is considered the standard of care for this condition [81]. Surgery is also indicated in patients with symptomatic compression on the basis of degenerative spine disease and/or a congenitally narrow spinal canal.

Vascular

No treatment of spinal cord infarct is proven effective, and management is supportive. In patients with evidence of spinal cord injury after aortic surgery, a protocol for hemodynamic augmentation of the blood pressure with vasopressors and use of lumbar drainage has been advocated. This strategy has not been validated in a clinical trial, but good outcomes have been reported with this protocol in patients presenting with delayed evidence of cord ischemia after surgery [82]. Similar treatment might be considered in patients with early cord ischemia due to other causes, but efficacy has not been established. There are a limited number of reports of successful use of catheter guided intra-arterial thrombolysis for cord infarction [83, 84]. The primary limitation of thrombolysis is the narrow window of opportunity for successful administration, especially considering the difficulties inherent in determining the etiology of an acute myelopathy and excluding contraindications to thrombolysis.

Dural arteriovenous fistulae and other spinal cord arteriovenous malformations should be treated with surgical or endovascular obliteration of the fistula. Improvement in functional status in these conditions can occur even when treatment has been delayed for up to several years [85].

Approach to Suspected Inflammatory and Other Myelopathies

Given the relative rarity of many causes of acute, noncompressive myelopathy and the difficult ethics of conducting controlled trials in patients with devastating acute neurologic conditions, there is a dearth of controlled clinical trial data for these disorders. We present a general approach to management in which empiric, early treatment is instituted while additional diagnostic studies are conducted to refine the diagnosis.

After cord compression has been excluded by neuroimaging, clinicians must decide whether the history, clinical presentation, and imaging are sufficient to define a particular diagnosis. Often, the diagnosis is not immediately apparent. In most of these cases, we advocate initial treatment with high-dose intravenous steroids (i.e., methylprednisolone 1 g IV daily for 5 days). Although this treatment is of unproven benefit for many causes of acute myelopathy, the treatment is regarded to be highly effective for transverse myelitis of a variety of causes. Even if the diagnosis of a primary inflammatory process is incorrect, corticosteroids may be beneficial in reducing inflammation and edema, and rarely would worsen the underlying disease process causing an acute myelopathy. Accordingly, most patients should be offered corticosteroid treatment empirically when an inflammatory myelopathy is being considered. In cases in which infectious etiologies are suspected, particularly bacterial and fungal infections, it is often best to defer steroid administration until the diagnosis of infection can be confirmed or refuted.

Patients who do not respond to initial steroid treatment and who do not have evidence of a noninflammatory disorder, such as cord infarction, may benefit from plasma exchange. A randomized, sham-controlled trial of plasma exchange in patients with severe attacks of acute CNS demyelination unresponsive to high-dose steroids demonstrated a 42.1% rate of moderate or greater improvement with plasmapheresis as compared to 5.9% for sham treatment [86]. Factors reported to predict a beneficial response to plasma exchange include male sex, preservation of reflexes, and early onset of treatment [87].

In patients who stabilize or improve, assessment for an underlying demyelinating disease should be conducted as described previously. Patients with features suggestive of multiple sclerosis or a high risk of developing this condition should be considered for immunomodulatory therapy. The institution of such therapies is not urgent and should be offered after careful consideration as to the nature of the underlying disorder, such as MS versus NMO. Patients with suspected MS are usually treated with interferon beta or glatiramer acetate, although other options are available. Patients who meet diagnostic criteria for neuromyelitis optica or those with a positive NMO-IgG antibody are at high risk for additional, clinically severe episodes of demyelination, and early institution of long-term immunosuppressant therapy for patients in these categories is indicated. Recommended therapies include azathioprine [88], mycophenolate mofetil [89], and rituximab [90]; there is insufficient evidence to establish whether one of these agents is superior as an initial treatment.

Patients with subacute myelopathy who are not improving with treatment and have no diagnosis after a thorough search for infectious and systemic inflammatory disorders may be candidates for biopsy of the spinal cord; the primary goals are to exclude malignancy and identify certain inflammatory disorders with characteristic histology (e.g., neurosarcoidosis). When neuroimaging is highly suggestive, empiric long-term corticosteroid treatment for a presumptive diagnosis of neurosarcoidosis may be appropriate without biopsy, but such decisions are difficult and risk missing an alternate etiology that requires different treatment. When a chronic inflammatory disorder such as sarcoidosis is identified, patients require initiation of treatment, usually with a prolonged course of moderate dose steroids (i.e., prednisone 1 mg/kg/day for six months).

Conclusion

The initial priority in assessment of an acute or subacute myelopathy is to obtain neuroimaging to determine whether cord compression is present. Patients with symptomatic cord compression

require urgent intervention, usually with surgical treatment. In patients with noncompressive cord signal abnormality, high-dose intravenous steroid therapy (i.e., methylprednisolone 1,000 mg IV for 5 days) is appropriate in most cases of idiopathic, inflammatory, or demyelinating myelopathy. Subsequent investigations are guided by the history and clinical response. Patients who improve or stabilize within 3 weeks often have an inflammatory demyelinating disease such as MS or NMO, a clinically isolated demyelinating syndrome, or idiopathic transverse myelitis. Brain MRI and CSF studies in these patients are helpful in determining the likelihood of future recurrence. In patients who continue to progress for greater than 3 weeks, one needs to consider neoplasm, certain chronic inflammatory disorders including sarcoidosis, and spinal stenosis. If a diagnosis cannot be determined despite thoughtful investigations and the patient continues to worsen, surgical biopsy may be required to determine the diagnosis and guide therapeutic intervention.

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Movement Disorder Emergencies

14

Robert L. Rodnitzky

Abstract

Movement disorders can be the source of significant occupational, social, and functional disability. In most circumstances the progression of these disabilities is gradual, but there are circumstances when onset is acute or progression of a known movement disorders is unexpectedly rapid. These sudden appearances or worsening of abnormal involuntary movements can be so severe as to be frightening to the patient and his family, and disabling, or even fatal, if left untreated. This chapter reviews movement disorder syndromes that rise to this level of concern and that require an accurate diagnosis that will allow appropriate therapy that is sufficient to allay anxiety and prevent unnecessary morbidity.

Keywords

Movement disorders • Emergencies • Acute Parkinsonism • Dystonia • Stiff person syndrome • Stridor • Delirium

Introduction

Movement disorders can be the source of significant occupational, social, and functional disability. In most circumstances the progression of these disabilities is gradual, but there are circumstances when onset is acute or progression of a known movement disorders is unexpectedly rapid. These sudden appearances or worsening of abnormal involuntary movements can be so severe as to be frightening to the patient and his family, and disabling, or even fatal, if left untreated. This chapter reviews movement disorder syndromes that rise to this level of concern and that require an accurate diagnosis that will allow appropriate therapy that is sufficient to allay anxiety and prevent unnecessary morbidity.

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Acute Parkinsonism

The sudden or subacute onset of significant parkinsonism, especially akinesia, is potentially very frightening to the affected patient and his/her family members. Of more concern is the potential for severe untreated akinesia to lead to serious

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complications, such as pulmonary embolism, aspiration, and pneumonia. Seven general etiologic categories of acute parkinsonism can be identified and the likelihood of arriving at the correct clinical diagnosis can be greatly enhanced by systematically considering which one or combination of these etiologies may be at play in a given acutely parkinsonian patient. The seven etiologic categories of acute parkinsonism are as follows (1) structural, (2) toxic, (3) impaired levodopa absorption, (4) iatrogenic, (5) infectious, (6) surgery, and (7) de novo (spontaneous acute parkinsonism).

Structural

The two most common structural causes of acute parkinsonism are stroke and hydrocephalus, although neither is extremely common in an absolute sense. Parkinsonism due to acute hydrocephalus is to be distinguished from the gradually evolving form of parkinsonism that can occur in patients with chronic hydrocephalus, especially normal pressure hydrocephalus. Acute parkinsonism can occur simultaneously with the development of acute hydrocephalus [1] but can also occur after shunt placement [2, 3] or shunt revision [4] in patients with long-standing hydrocephalus. The rapid onset of parkinsonism in acute hydrocephalus is probably due to direct compression or shearing force on the substantia nigra secondary to changing pressure dynamics of the rapidly enlarging ventricles [5]. Parkinsonism due to shunt revision or placement is due to rapidly shrinking ventricles with subsequent midbrain distortion [2]. The simultaneous occurrence of other signs of rostral midbrain dysfunction, along with parkinsonism, after shunting supports the notion that the postshunting findings are all due to mechanical distortion of the midbrain [6]. In patients whose akinesia appears to be related to acute hydrocephalus with acutely enlarging ventricles, shunting is indicated and could be lifesaving. Parkinsonism might be improved by this intervention, or as mentioned above, could be exacerbated. In parkinsonism related to acute hydrocephalus, persistent hydrocephalus, or to shunt revision, levodopa therapy is usually effective both in the short term and chronically [2, 4–6].

Acute cerebral infarction involving the striatum or the substantia nigra is another structural insult that can result in acute parkinsonism. The common term "vascular parkinsonism," as used today, refers to the gradual appearance of parkinsonian features, usually a parkinsonian gait, due to diffuse, bihemisphere small vessel ischemic disease. Large artery infarctions, on the other hand, produce unilateral or bilateral parkinsonism over a matter of days to months. When a striatal infarction is associated with significant hemiparesis, unilateral parkinsonism typically evolves once the hemiparesis begins to improve [7]. Striatal infarctions are relatively common, but only a small percentage result in parkinsonism [8]. Parkinsonism can also develop after infarction of the substantia nigra [9]. Infarction of the pedunculopontine nuclei in the brainstem can cause acute onset of gait freezing, similar to that seen in Parkinson's disease [10]. Therapy of infarction-related parkinsonism with levodopa is most effective in those cases where the pathology is in, or close to, the substantia nigra [11]. Somewhat paradoxically, stroke involving the tuberothalamic artery can improve parkinsonian tremor, presumably through damage to the ventrolateral thalamic nucleus, similar to the lesion of a therapeutic thalamotomy [12], or deep brain stimulation of this structure.

Toxic

A variety of nonindustrial toxins can also cause acute parkinsonism. The more common toxic exposures that might present to a community Emergency Department are discussed here. Organophosphate insecticides, either through inadvertent ingestion on food or exposure in an agricultural setting, can cause acute, reversible parkinsonism. In these cases, treatment with levodopa [13] has been less effective than amantadine [14] and dopamine agonists [15]. Carbon monoxide (CO) poisoning results in subacute parkinsonism. In a large series of 242 CO poisoning

cases, 10% of the individuals affected developed parkinsonism with a latency of 2–26 weeks (median 4 weeks) after the acute exposure [16]. Imaging of the brain in these patients reveals evidence of bilateral pallidal necrosis with symmetric hypodensity on CT scan and high signal intensity on FLAIR and T2-weighted MRI sequences [17]. There is, however, not a complete correlation between the appearance of pallidal necrosis on CT or MRI and parkinsonism in CO poisoning. Of 17 patients with CO-related parkinsonism in one series, only 47% had abnormal CT scans [16]. In this series, levodopa and anticholinergic drugs were not effective, but 81% of affected individuals recovered gradually over a 6-month period of time. Initial hyperbaric oxygen therapy of CO poisoning in the acute phase may reduce subsequent neurologic sequelae, but controlled studies of this therapeutic approach are still lacking [18]. Purposeful or accidental ingestion of ethylene glycol or methanol can result in acute parkinsonian akinesia, often associated with hemorrhagic necrosis of the basal ganglia [19]. Levodopa therapy can improve the rigidity and bradykinesia associated with these two toxic exposures [19].

Impaired Levodopa Absorption

Gastric emptying is commonly slightly delayed in PD patients, but superimposed gastrointestinal disorders can further delay passage of levodopa through the pylorus resulting in a significant decrease in levodopa absorption in its main absorptive site in the jejunum. The consequence of such an acute or subacute decrease in levodopa absorption is an acute increase in parkinsonian symptoms, including akinesia. In these cases, identification and treatment of the comorbid gastrointestinal disorder is the first therapeutic measure that should be taken. In a review of 146 non-parkinsonian patients with acute gastroparesis, the three most common associated clinical features were abdominal pain, depression on antidepressant therapy, and gastroesophageal reflux [20]. Should recent onset or worsening of any of these comorbid conditions be present in the acutely akinetic PD patient, gastroparesis with resultant impaired levodopa absorption should be strongly suspected. Gastroparesis in PD patients has also been reported in the presence of acute duodenal ulcer and intestinal volvulus [21]. In addition to treating the primary medical cause of delayed gastric emptying, prokinetic agents can be useful to reduce gastric stasis. Domperidone, a peripheral dopamine receptor antagonist, is useful for this purpose but is not yet approved in the USA. Administering levodopa with a carbonated and/or caffeinated beverage may enhance passage of levodopa through the stomach and enhance absorption. Replacing an oral dopamine agonist with a transdermal agent, such as rotigotine [22] (if available), would be useful. For very severe absorptive dysfunction with significant akinesia such as after gastrointestinal surgery, subcutaneous apomorphine may prove useful [23], although in this circumstance, some patients become relatively refractory to all dopaminergic agents, including apomorphine [21].

Iatrogenic

The inadvertent or ill-advised use of drugs that are dopamine receptor blocking agents (DRBA) can rapidly result in a severely exacerbated parkinsonian state in PD patients. Occasionally, non-PD patients or PD patients not yet known to have clinically apparent PD can be rendered acutely or subacutely akinetic by the administration of DRBAs, particularly if used at a high dosage. Among DRBAs, the typical antipsychotic agents, such as haloperidol, have the greatest potential to cause significant akinesia, but other classes of dopamine antagonists, including most of the atypical antipsychotic agents and the DRBA antiemetic drugs, such as prochlorperazine and metoclopramide, have this potential as well [24]. The most serious iatrogenic forms of acute akinesia are neuroleptic malignant syndrome (NMS) and the closely related condition known as parkinsonism-hyperpyrexia syndrome (PHS), as these conditions, left untreated, can result in major disability and are potentially fatal. Serotonin syndrome shares some clinical features with NMS, including some parkinsonian phenomena.

NMS is an acute reaction that can occur either as a result of treatment with a dopamine blocking agent [25], or after rapid withdrawal or reduction of one or more dopaminergic drugs in a Parkinson's disease patient, in which case it is referred to as parkinsonism-hyperpyrexia syndrome (PHS) [26]. PHS can also occur in other forms of parkinsonism, such as progressive supranuclear palsy or multiple system atrophy (MSA) [27]. The onset of NMS is usually within a month after beginning DRBA therapy or an increase in dosage, but as many as 16% of cases of NMS begin within the first 24 h of therapy and 30% by 2 days [25]. PHS developing in Parkinson's disease patients usually presents shortly after the discontinuance or reduction of a dopaminergic medication [26]. In one series, PHS occurred at a mean of 93 h after medication withdrawal [28]. All neuroleptic drugs can cause NMS, as can all atypical antipsychotic agents [29–32]. The overall incidence of NMS appears to be lower in patients receiving atypical antipsychotic agents, and at least in the case of clozapine [33], olanzapine [34], and risperidone [31], a milder syndrome with less prominent fever or rigidity [35] and less elevation of creatinine kinase may develop. However, in one recent review of the literature [36], 68 reported cases of NMS were related to atypical antipsychotics, and in this survey, clozapine was associated with NMS as often as other atypical agents, suggesting that low extrapyramidal syndrome-inducing potential does not necessarily reduce the occurrence of NMS. Antiemetic DRBAs, such as metoclopramide and prochlorperazine, can also result in NMS [37]. Antidepressants, including tricyclics [38], selective serotonin reuptake inhibitors [39], and lithium [40], either alone or in combination, have all been reported to cause a syndrome resembling NMS, but such cases are uncommon and often the clinical presentation is atypical or indistinguishable from serotonin syndrome. Although discontinuance of any Parkinson's drug can result in PHS, stopping levodopa is the most common cause. NMS is more likely to occur in young patients, in males, and in patients who are agitated, dehydrated, have received large rapidly administered dosages of the offending drug, or who have had previous electroconvulsive therapy [41, 42]. Elevation of serum creatine kinase during a previous psychotic episode unassociated with NMS may be a risk factor for NMS developing during future administration of DRBAs [43].

In addition to dehydration, risk factors for PHS include several characteristics of the underlying parkinsonism. Thus, more severe parkinsonian symptoms, longer disease duration, a history of "wearing off," and a history of an early age of parkinsonism onset are risk factures for PHS [44]. Serious PHS has occurred after perioperative withdrawal of antiparkinsonian medications [45]. PHS has also been reported in Parkinson's patients who abruptly discontinued fava bean ingestion, which was being taken for its levodopa content [46]. The syndrome has also occurred in Parkinson's patients during extreme periods of ambient heat even in the absence of medication withdrawal [47]. Acute akinesia related to levodopa resistance after a surgical procedure resembles PHS [21].

The cardinal clinical manifestations of NMS and PHS are virtually identical and include fever, muscular rigidity, autonomic instability, and confusion or alteration in consciousness [37]. Among autonomic symptoms, tachypnea, tachycardia, labile blood pressure, diaphoresis, and urinary retention are most common [48]. The most frequent movement disorder in NMS is rigidity, which is often preponderantly axial. Other movement disorders are possible, including dystonia and chorea. Fever is typically at least 38°C and often higher. Creatine kinase levels are usually above 2,000 IU/L and often in the range of 15,000–20,000 IU/L [49, 50]. The white blood cell count is often elevated, but usually without a left shift. Milder or atypical forms of the syndrome without one of the classic features, such as muscle rigidity [51] or fever [31, 52], may exist. Cases without rigidity may simply present as a fever of unknown origin [53]. PHS is especially likely to present with fever as the first symptom [27].

The treatment of NMS and PHS should be considered emergent, especially in cases in which all of the clinical criteria are fulfilled or in patients with extremely high fever and rhabdomyolysis.

In these cases, there can be serious morbidity and occasionally a fatal outcome. The most common complications affecting the prognosis are cardiac failure, cerebellar degeneration, respiratory disturbances, and renal failure, the latter of which can be associated with disseminated intravascular coagulation and rhabdomyolysis [54, 55]. The first therapeutic measure that must be taken is discontinuing the offending neuroleptic or other causative dopamine blocking drug, or in Parkinson's patients with PHS, replacing a recently withdrawn or altered dopaminergic drug. Supportive measures, such as hydration and lowering of fever, must be started early. Anticholinergic drugs should be discontinued in Parkinson's disease patients, since they inhibit heat dissipation. Tapering anticholinergics is advised rather than abrupt cessation to avoid rebound rigidity. Respiratory support may be needed because of severe rigidity of respiratory muscles. Cardiac arrhythmias and blood pressure abnormalities must be treated [56]. In patients with dangerously high body temperature, antipyretics such as aspirin are usually ineffective, but a noninvasive body surface cooling device (Arctic Sun®, MediVance Inc.) can be very useful to reverse hyperthermia [57].

The specific first-line medical therapies for NMS include bromocriptine, orally or by nasogastric tube, dantrolene, and amantadine [37]. Bromocriptine is administered in an initial dosage of 2.5 mg every 4 h, being careful to observe for induction or worsening of hypotension. The dose can be increased daily, if required, to as much as 50 mg per day. An alternative dopamine agonist is subcutaneous apomorphine, which can produce a rapid clinical response [58, 59]. Dantrolene can be administered intravenously, if needed, in a dosage of 1–10 mg/kg/day in three divided dosages. Most patients will require dosages in the lower part of this range [60]. Dantrolene is a good choice for initial therapy alone or in combination with bromocriptine when there is severe rigidity and rhabdomyolysis. Carbamazepine is a possible second-line therapy [61]. None of these medical therapies have been proven to be effective by prospective studies, but rather derive their reputation for efficacy from case reports and small series culled from the literature. However, a large retrospective review of 734 cases of NMS concluded that treatment with bromocriptine, dantrolene, or amantadine reduced mortality more than supportive care alone [62]. For NMS cases that are refractory to medical therapy, electroconvulsive therapy has been found to be useful in both adults and children [63], as well as in the PHS [64].

Recovery from NMS typically occurs over a 1- to 2-week period, but resolution after recovery from the acute phase may be delayed in those having received long-acting depot neuroleptics. Some sequelae, especially neuropsychiatric symptoms, can persist for weeks or months [65]. Pulse methylprednisolone therapy has been reported to significantly shorten the recovery phase in patients with Parkinson's disease [66]. Rechallenge with neuroleptics after recovery results in reoccurrence of NMS in less the 15% of cases. To minimize the likelihood of reoccurrence, rechallenge should be delayed for at least 2 weeks after recovery and a lower potency neuroleptic agent or atypical antipsychotic drug should be used.

Serotonin syndrome (*SS*) has become increasingly more common, reflecting the increased number and increased use of serotonergic medications. This pattern of increased use also includes the pediatric population. In a survey of North Carolina Medicaid prescriptions, the prevalence of prescriptions for SSRIs in the 6–14-year-old age group increased sevenfold from 0.2% to 1.5% between 1992 and 1998 [67]. This syndrome, like NMS, includes involuntary abnormal movements, especially myoclonus and tremor, and as such is considered a movement disorder emergency. As the name implies, serotonin syndrome occurs in patients receiving one or more serotonergic drugs. There are two commonly utilized diagnostic criteria for serotonin syndrome, the Sternbach Criteria [68] and the Hunter Serotonin Toxicity Criteria [69]. Using the Sternbach Criteria, there are three requirements:

(a) After the addition of or increase in dosage of a serotonergic agent, at least three of the following clinical features must be present: agitation, mental status changes, myoclonus,

hyperreflexia, diaphoresis, shivering, tremor, diarrhea, incoordination, and fever.

(b) Other etiologic causes (infectious, metabolic, substance abuse or withdrawal) have been ruled out.

(c) An antipsychotic has not been started or increased in dosage before the onset of the symptoms.

To fulfill the Hunter Serotonin Toxicity Criteria, the patient must have taken a serotonergic agent and meet one of the following requirements:

(a) Exhibit spontaneous clonus

(b) Have inducible clonus plus agitation or diaphoresis

(c) Exhibit ocular clonus plus agitation or diaphoresis

(d) Have hypertonia

(e) Have a temperature greater than 38°C plus ocular clonus or inducible clonus

Both sets of criteria are useful, but a comparison of their utility in patients with an established serotonin syndrome diagnosis suggested that the Hunter Criteria was more sensitive than the Sternbach Criteria (84% vs. 75%), and minimally more specific (97% vs. 96%) [69].

The clinical signs of serotonin syndrome resemble those of NMS and in many cases the two syndromes appear to overlap in the same patient [70]. For determining proper therapy, distinguishing the two syndromes from one another is very important, since their respective medical therapies are distinct. Both syndromes include mental status changes, fever, autonomic dysfunction, and a variety of movement disorders, but the relative severity of these signs in the two syndromes can be a differentiating factor. Compared to NMS, in serotonin syndrome, fever, elevation of creative kinase, and alteration in sensorium are generally less prominent, while myoclonus, gastrointestinal symptoms, a shivering-type tremor, hyperreflexia, clonus, and pupillary dilatation are more prominent. Among these differences, hyperreflexia with clonus, the presence of otherwise unexplained myoclonus, and a rapid onset (within hours of the offending pharmacologic event) are among the most useful clues that the patient is suffering from serotonin syndrome, rather than NMS. A comparison of common features of serotonin syndrome, NMS, and features that most accurately discriminate the two syndromes from one another is shown in Table 14.1.

Table 14.1 Serotonin syndrome. Comparison with neuroleptic malignant syndrome

	SS	NMS
Mental status change	+	++
Fever	++	+++
Tachypnea/tachycardia	++	+++
Diarrhea	+++	0
Diaphoresis	++	+++
Rigidity/bradykinesia	0	+++[a]
Stupor	+	+++[a]
Tremor	+++[b]	+
Shivering	+++[b]	0
Myoclonus	+++[b]	+
Hyperreflexia/clonus	+++[b]	0
Elevated CK	+	+++[a]
Pupillary dilation	++	0
Acute onset	+++[b]	+

[a]Important differentiating feature of neuroleptic malignant syndrome (NMS).
[b]Important differentiating feature of serotonin syndrome (SS).

Misdiagnosis, especially early in the course of serotonin syndrome, is common. For example, the presence of hyperreflexia and clonus can lead to the false impression of a pyramidal syndrome and the presence of diarrhea plus fever can lead to the incorrect diagnosis of an infectious gastroenteritis [71].

The offending therapies that have the potential to contribute to serotonin syndrome fall into one of the following seven pharmacologic categories (Table 14.2). Although serotonin syndrome is thought to result from stimulation of 5-HT_{1A} and 5-HT_{2A} receptors [73], some drugs that stimulate other classes of receptors, such as most triptan agents, probably can contribute to the development of serotonin syndrome.

Although any of these drugs and treatments taken alone can cause serotonin syndrome, the risk is greatest when two or more serotonergic therapies are administered simultaneously [74, 75]. The greatest risk is in those receiving a nonselective MAO inhibitor along with a potent serotonin reuptake inhibitor [76]. Higher dosages of

Table 14.2 Agents that can cause serotonin syndrome

1.	Inhibitors of serotonin reuptake: all of the SSRIs, SNRIs several tricyclic antidepressants, dextromethorphan, amphetamine, cocaine, MDMA (ecstasy), St. John's wort
2.	Inhibitors of serotonin metabolism: selective MAO-B inhibitors (selegiline or rasagiline), non-selective MAO inhibitor antidepressants, non-selective MAO inhibitor antibiotic (linezolid)
3.	Agents that increase serotonin synthesis: L-tryptophan
4.	Enhancers of serotonin release: amphetamines, cocaine, fenfluramine, MDMA (ecstasy)
5.	Serotonin agonists: buspirone, triptans, ergotamines
6.	Non-specific enhancers of serotonin activity: lithium, electroconvulsive therapy
7.	Serotonergic effect, mechanism is uncertain (methylene blue)

Adapted from Lane R, Baldwin D [72].

these medications also increase the risk and the severity of the syndrome. For example, several cases of serotonin syndrome in children have resulted from accidental ingestion of a large and pharmacologically excessive amount of a parent's medication [77, 78]. Methylenedioxymethamphetamine (MDMA), also known as "ecstasy," is an amphetamine-derived street drug that is commonly used by high school and college students, especially while attending drug-inspired dance gatherings known as "raves" [79] during which there is a high ambient temperature and vigorous physical activity leading to dehydration. This drug has serotonergic properties and either alone or in combination with other serotonergic drugs can produce a syndrome with features of serotonin syndrome [70]. Fatalities have occurred due to MDMA-related serotonin syndrome, often associated with delayed diagnosis in part due to unawareness of the history of illicit drug ingestion. Purposefully combining MDMA with an MAO inhibitor to enhance its effect has proven especially lethal [80]. In the United Kingdom, 605 ecstasy-related deaths were reported in a 7-year period [81]. Generally, what contributes to a potential fatal outcome in serotonin syndrome is the development of rhabdomyolysis, myoglobinemia, and renal failure. Acute myocardial infarction has also occurred in the setting of serotonin syndrome [82].

Of interest to neurologists are the risks associated with some serotonin-enhancing drugs that are commonly used in neurologic practice, including antimigraine agents, such as triptans and dihydroergotamine, and the selective MAO-B inhibitors, selegiline and rasagiline, used in Parkinson's disease. Serotonin syndrome was reported in only 11 patients receiving a triptan alone in the FDA adverse event reporting system [83]. However, triptans taken along with other serotonergic agents, especially the commonly used SSRIs, have been reported to cause the serotonin syndrome [84]. In 2006, the FDA issued an alert concerning the potential of serotonin syndrome in patients taking triptans and SSRIs or SNRIs, based on 29 reported cases. Subsequent analysis of these cases has suggested that the risk is very small, and in fact not all of the FDA cases may have met the diagnostic criteria for serotonin syndrome [85, 86]. In regard to selegiline, there is concern that this agent could cause the serotonin syndrome in patients also receiving other serotonergic drugs. Despite this concern, there are very few well-documented cases of this interaction, and a similar level of risk seems likely for the newer selective, irreversible MAO-B inhibitor, rasagiline. Recently, it has become apparent that the widely used antibiotic linezolid is an MAO inhibitor that can cause serotonin syndrome when used along with other serotonergic drugs [87].

Prevention is very important in the serotonin syndrome. To avoid an interaction leading to serotonin syndrome, there should be a period of at least 2 weeks between stopping an SSRI and starting an MAO inhibitor, and approximately 5 weeks after discontinuance of fluoxetine, which has a much longer half-life. Treatment of the acute serotonin syndrome begins with the discontinuation of all serotonergic medications. This strategy alone will often result in resolution of the syndrome within 24 h. When symptoms are

particularly resistant or severe, begin direct medical therapy with the serotonin antagonist, cyproheptadine in a dosage of 8 mg [72, 88]. It has been suggested that reversal of mydriasis within an hour of cyproheptadine is a useful indication that the drug is working [89]. Rehydration and control of fever are important in the presence of severe hyperthermia. A noninvasive cooling device (Arctic Sun®) can be used to lower body temperature similar to its use in NMS [57]. Antipyretic agents, such as aspirin and acetaminophen, are not effective for lowering fever of this origin. In the presence of severe muscle rigidity, dantrolene can be used. Chlorpromazine has been suggested as a therapy for serotonin syndrome, but its use depends on absolute certainty that the patient does not have NMS instead, which might be worsened by this therapeutic approach.

Drug-induced parkinsonism: Administration of dopamine blocking drugs, including typical antipsychotic agents, atypical antipsychotic agents, and dopamine blocking antiemetics can all cause rapid-onset parkinsonism, especially when administered in high dosages [24]. A large number of other drugs that are not primary dopamine blocking agents, such as selective serotonin uptake inhibitors, valproic acid, amiodarone, and certain chemotherapeutic agents, rarely cause severe de novo parkinsonism and can also occasionally significantly exacerbate parkinsonian symptoms in a known PD patient [90]. The calcium channel blockers, cinnarizine and flunarizine, neither marketed in the USA, can cause parkinsonism due to their significant dopamine blocking capacity. Drug-induced parkinsonism can resemble ordinary Parkinson's disease, although there is a tendency for less tremor and more symmetry in the drug-induced syndrome. Some patients with drug-induced parkinsonism actually have Parkinson's disease that has been uncovered by the administration of the offending drug. These patients may be even more susceptible to drugs that are less obvious dopamine blockers such as selective serotonin uptake inhibitors [91]. SPECT imaging of the dopamine transporter can be used to help determine whether a drug has caused transient parkinsonism or has uncovered latent Parkinson's disease [91]. The initial treatment of drug-induced parkinsonism is to discontinue the offending drug, if medically feasible. Discontinuance may not always be possible in the case of effective antipsychotic agents used to treat a serious psychiatric condition. Even with discontinuance, improvement in parkinsonism cannot be expected for days to weeks and occasionally several months. Once the offending drug has been discontinued, immediate medical therapy begins with anticholinergic agents or amantadine. If these are not effective, then a course of levodopa can be considered with appropriate caution regarding the exacerbation of psychosis that this treatment can cause. The parkinsonism caused by chemotherapy agents can be dramatically responsive to levodopa [92].

Infection

Any intermittent infection, whether viral or bacterial, can exacerbate ongoing parkinsonian symptoms, especially in moderately or severely advanced PD patients. A recent survey of PD patients admitted to the hospital confirmed that infection was the most common reason for admission, and among infections, pneumonia was most common followed by urinary tract infection [93]. Occult infection, especially pneumonia or urinary tract infection, should always be considered in PD patients presenting with unexplained worsening of symptoms.

Acute or subacute parkinsonism has been reported as a complication of several different forms of viral encephalitis including encephalitis due to Herpes Simplex Virus-1, West Nile virus, Coxsackieviruses, St. Louis encephalitis virus, and HIV [94–96]. A major clue to this etiology of acute parkinsonism is the recent history or concurrent presence of seizures, fever, or extreme somnolence. Standard antiparkinsonian drugs, such as trihexyphenidyl and carbidopa/levodopa, may improve parkinsonian symptoms during the acute phase of a viral illness [95]. Encephalitis lethargica, which occurred as a pandemic in the early twentieth century, is a well-accepted cause of parkinsonism, and although rare, still does

occur [97]. The presence of antineuronal antibodies and the absence of positive viral PCR in parkinsonian patients with encephalitis lethargica suggest that the parkinsonism is due to an autoimmune condition rather than an acute viral illness, and may require immunomodulatory therapy [98]. Another form of infection that can lead to autoimmune akinesia is parkinsonism after streptococcal infection with associated antibasal ganglia antibodies [99].

The treatment of infection-related forms of parkinsonism is to first treat the underlying viral or bacterial infection with appropriate antiviral agents or antibiotics. For the parkinsonian features themselves, standard antiparkinsonian therapy such as levodopa is often effective [95, 100]. Those infections associated with antibasal ganglia antibodies may respond to immunomodulatory therapy, such as corticosteroids [99].

Surgery

Parkinson's disease patients undergoing major surgery commonly note worsening of their symptoms in the postoperative period. Most often, the degree of worsening is mild or moderate, but occasionally it can be severe and associated with profound akinesia [21]. While any type of surgery can have this effect, joint surgery is one of the more common precipitants of postoperative PD worsening. This syndrome appears to be independent of abnormalities of levodopa absorption and in its most severe form, is associated with refractoriness to all dopaminergic agents [21]. Despite concern for refractoriness to dopaminergic agents, therapy with oral levodopa or nonoral dopaminergic agents, such as subcutaneous apomorphine or transdermal rotigotine, should be attempted if either is available. Should there be no benefit from these agents, supportive care for the immobilized patient is paramount until responsiveness to medication resumes, often in 2–7 days. It is wise to foreworn PD patients undergoing elective surgery that some worsening is likely to occur in the postoperative period in order to minimize personal and family anxiety over this occurrence.

Another potential cause of acute akinesia in the postoperative period is enteral nutrition [101]. This phenomenon is largely the result of persistent interference with levodopa absorption by the high-protein content of continuous tube feedings. It can be combated by changing from continuous to intermittent bolus enteral feedings and staging levodopa dosages in between and temporally distant from boluses of tube feedings.

For PD patients undergoing planned or elective operations, the surgical team should be forewarned to avoid administering dopamine blocking antiemetics or antipsychotic drugs in the postoperative period, if at all possible, since these agents can further exacerbate postoperative parkinsonism. In place of the dopamine blocking antinausea drugs (such as droperidol, prochlorperazine, or metoclopramide), domperidone (not available in the USA) or trimethobenzamide should be used instead.

De Novo Parkinsonism

There is one form of degenerative parkinsonism that typically has an acute or subacute onset. Rapid-onset dystonia-parkinsonism (RDP) is an autosomal dominant condition in which both dystonia and parkinsonism develop as rapidly as over a few minutes to as long 30 days [102]. In this condition, parkinsonian symptoms, such as bradykinesia and hypophonia, pursue a rostral–caudal pattern of progression. RDP can be differentiated from idiopathic PD by its sudden onset, its initial rapid progression, the rostral–caudal progression, and the absence of tremor. Family history, if present, is useful, but the autosomal dominant gene in this condition displays variable penetrance. Another somewhat helpful differentiating feature from PD is that the great majority of patients with RDP are under the age of 30, and in fact, almost half are under the age of 20 [102]. A variety of triggers leading to the initial clinical presentation have been reported in this condition including fever, trauma, and psychiatric events, the latter sometimes falsely raising the possibility of psychogenic parkinsonism. Typically, these patients' parkinsonian symptoms

are refractory to dopaminergic therapy [103]. While pharmacologic therapy of this form of acute parkinsonism is not very effective, patients can be reassured that in the majority of cases most of the symptoms are minimally progressive after the initial presentation, with only a small number of patients experiencing a second later episode of abrupt worsening.

Severe or Acute Levodopa-Induced Dyskinesias

Parkinson's disease patients are susceptible to severe medication-induced dyskinesias that can be choreic, dystonic, or both. These involuntary movements are usually a complication of dopaminergic medications and can be further exacerbated by levodopa enhancing preparations such as COMT inhibitors or MAO inhibitors. Dyskinesias related to levodopa and/or dopamine agonist medications typically remit spontaneously given sufficient time, but if the involuntary movements are of extremely high amplitude or involve many body parts simultaneously, they can prove to be frightening and/or exhausting to the patient and to family members, resulting in an Emergency Department visit. For example, these movements can be sufficiently prolonged and severe to result in a significant elevation of plasma creatine kinase [104].

Under these circumstances, the causative medication(s) should be temporarily suspended with a plan to reintroduce them at a slightly lower dosage once the dyskinesias have remitted. It is probably unwise to entirely discontinue chronically administered dopaminergic medicines for any sustained period of time for fear of inducing the PHS and to avoid producing severe prolonged akinesia. If there is not an immediate reduction in the severity of the dyskinetic movements, then medical therapy will be required in the emergency room setting. Benzodiazepine preparations such as diazepam, lorazepam, or clonazepam can be very helpful, both in relieving the severity of the dyskinesias and diminishing the associated anxiety that accompany them. Often a parenteral route of administration provides more rapid relief. If swallowing is intact and the patient has already ingested a controlled release levodopa preparation, administration of a high-protein snack can be attempted in the hope of limiting further gastrointestinal absorption of levodopa and inhibiting its passage across the blood–brain barrier through competition for the active transport system for large neutral amino acids [105]. If it is necessary to restart dopaminergic medications at the same dosage to control parkinsonian symptoms, strategies to reduce the potential for recurrent severe dyskinesias should be employed including adding amantadine for its antidyskinesia effect and replacing levodopa partially or completely with a dopamine agonist, since this class of agents has a lower potential to cause dyskinesias.

Acute Behavioral Change in Parkinsonism: Psychosis, Delirium Panic Attack

A variety of behavioral abnormalities can occur in PD. The most common, dementia, is gradual in evolution and is not typically viewed as an emergency, but many other behaviors can appear suddenly, especially in the chronically demented PD patient. These conditions can result in emergency room visits, emergency inpatient consultations, or involvement by security or law enforcement officials.

Psychosis

Psychosis in PD commonly results in visual hallucinations, delusional thoughts, and illusory phenomena. Auditory and tactile hallucinations can occur, but are much less common. Psychosis typically appears in PD patients with cognitive impairment, but can also occasionally be seen in nondemented patients. Psychotic symptoms can be rapid in appearance or escalation, suddenly reaching a critical point in severity and resulting in an emergency presentation. The most common emergency presentations are hallucinations that are frightening to the patient or delusions that are threatening. Both have the potential to result in a

state of agitation. In these circumstances, reassurance may be somewhat helpful, but in the most severe cases is inadequate. Delusions of harm from family or friends or hallucinations of intruders in the home may result in calls from the patient to police or other emergency responders. Recognizing that medications are often a contributing cause of acute psychosis, recent additions or dosage increases in antiparkinsonian drugs, or other medications, particularly those with anticholinergic properties, should be evaluated and at least temporarily discontinued if needed. Pharmacologic therapy will often be required for more immediate relief of psychotic symptoms, especially in the emergency room setting. The atypical antipsychotic agents are useful in reversing psychotic symptoms in PD. Clozapine is the most useful, but has potentially serious adverse effects, including agranulocytosis, and should not be administered emergently without a thorough review of possible previous administration and adverse effects, a process that cannot be easily accomplished quickly in the emergency room setting [106]. The next most useful and commonly used atypical antipsychotic agent is quetiapine [107]. Although some studies have questioned its efficacy [108], common experience supports its benefit. The only atypical antipsychotic agents readily available in parenteral form for acute administration are olanzapine and ziprasidone. Olanzapine in effective dosages worsens parkinsonism and is not a good choice, whereas ziprasidone has less potential to exacerbate parkinsonian symptoms and early experience suggests that when administered intramuscularly, it can improve acute psychotic symptoms within 1–2 h [109, 110]. The use of atypical antipsychotic agents should be tempered by the "black box" warning of a slight increased risk of death when used to treat elderly patients with dementia [111].

Panic

Anxiety is common in PD. Most forms such as generalized anxiety or social phobia seldom present as an emergency, but panic attacks, which are not uncommon in Parkinson's disease, may result in an emergency room visit. A recent study of anxiety disorders in PD found a lifetime prevalence of 49% of all forms of anxiety, whereas the specific prevalence of panic disorders in PD patients was 10% [112]. Panic disorder is more likely to appear in patients with an earlier age of PD onset and in those with a family history of parkinsonism [112].

Typical panic attack symptoms include an intense discomfort or fear with sudden onset of associated symptoms such as a sense of impending death, choking, breathlessness, palpitations, or chest pain. A panic attack sometimes is associated with the "off" state in PD. In that circumstance, pharmacologic measures to reverse the parkinsonian "off" state will also improve the sense of panic. When readjustment of antiparkinsonian medications to correct the off state does not reverse a panic attack, anxiolytic therapy will be required. A short-acting, rapid-onset benzodiazepine, such as alprazolam, is useful for reducing the intensity of panic-associated symptoms. Selective serotonin reuptake inhibitors are also useful for panic disorders, but the absence of a rapid-onset formulation makes them less useful for acute panic attacks in the emergency setting than for the treatment of an ongoing panic disorder.

Delirium

The most common causes of acute delirium in PD are intercurrent illness (especially infection), or the postoperative state. When an identifiable infection is present, appropriate antibiotic therapy will aid reversal of delirium. Any form of surgery, especially orthopedic procedures, may result in postoperative delirium. The greatest risk for postoperative delirium is preexistent dementia. In anticipation of the possibility that delirium may develop postoperatively in such patients, certain preventative measures are useful. Thus, in PD patients with known dementia, the use of regional rather than general anesthesia and employing less deep levels of sedation are useful strategies that can lessen the risk of delirium after surgery [113, 114].

In addition to treating concurrent illnesses, such as infection, environmental methods to reestablish normal day, night, place, and time orientation should be employed. Encouraging a family member to sit with the patient and provide a focus of orientation can be useful in this regard. In the severely agitated patient, pharmaceutical management will more likely be required. Whereas haloperidol is standard therapy for delirium, it cannot be used in PD patients without severely worsening their parkinsonism. An atypical antipsychotic agent, preferably quetiapine, should be used instead [115, 116]. In some non-PD populations, the alpha-2-agonist dexmedetomidine has been shown to be more effective in treating delirium than either lorazepam [117] or haloperidol [118]. There are no apparent contraindications to the use in PD of this agent [119].

Suicide

One final behavioral emergency in PD is suicidal ideation, which has been estimated to occur in as many as one third of PD patients [120]. The suicide rate is especially high in PD patients having undergone deep brain stimulation of the subthalamic nucleus (STN). A recent meta-analysis found that suicide attempts were observed in 1% of STN DBS patients and successful suicides were documented in 0.5% [121]. These data point out that suicidal thoughts, gestures, and attempts in PD patients, especially in DBS patients, are true emergencies and appropriate psychiatric consultation is required in these patients, with consideration of admission to the hospital and need to be taken very seriously.

Inspiratory Stridor in Multiple System Atrophy

MSA can be associated with inspiratory stridor. Whether stridor in this clinical condition is due to laryngeal abductor weakness or adductor dystonia is uncertain, but the potential of a fatal outcome due to narrowing of the inspiratory pathway, if left untreated, is without question. While stridor is more common in moderately or severely advanced MSA patients, it can occasionally be among the presenting signs of this condition [122]. An early clue to the presence of stridor may be peculiar high pitched, nonposition dependent snoring during sleep. In many patients, this may be the exclusive time of day that stridor occurs. Laryngoscopy is the definitive diagnostic technique for identifying laryngeal abductor dysfunction, and in patients with stridor that occurs exclusively at night, the procedure may have to be performed during sleep to identify the problem. Some patients experience stridor during the daytime as well as the night, which is even more ominous in terms of the potential for serious respiratory embarrassment. One study suggested that MSA patients who develop daytime stridor have a mean survival of less than 1 year [123]. Since stridor has been associated with sudden death in MSA patients, it is truly an emergency that requires immediate therapeutic attention. Rarely, stridor can be seen in other movement disorders, including Parkinson's disease, Creutzfeldt–Jacob disease, and Machado–Joseph disease [124].

The simplest therapy for stridor associated with MSA is CPAP [125]. Nocturnal videolaryngoscopy has documented that CPAP is capable of producing separation of the adducted vocal cords and improvement of stridor [126]. In more advanced patients, where there may also be central hypoventilation, BIPAP has been suggested as the preferred therapy instead [127]. Should none of these approaches be practical or successful, or if there is daytime stridor, tracheostomy, the most definitive therapy, is required [125]. Precipitation or exacerbation of central sleep apnea has been reported to occur after institution of tracheostomy in some MSA patients, occasionally with a fatal outcome [128]. Some deaths during sleep have also been reported in MSA patients despite adequate CPAP therapy, and in these cases concurrent autonomic dysfunction is suspected to have resulted in a cardiac demise [129].

Acute Dystonic Reaction

Acute dystonic reactions (ADR) typically occur after exposure to DRBA. Neuroleptic agents such as haloperidol, or antiemetic agents such as

prochlorperazine are the most common offending agents. Over 50% of ADRs occur within 24 h after DRBA exposure and approximately 90% occur within 5 days [130]. In the typical clinical presentation, the muscles of the mouth, face, eyes, and neck are involved resulting in one or more dystonic manifestations such as retrocollis, back arching, lateral flexion of the trunk, trismus, tongue protrusion, or deviation of the eyes [131]. Trismus can be severe enough to dislocate the jaw. A potentially fatal form of ADR is dystonic laryngospasm with compromise of the airway [130, 132]. This must be correctly identified and distinguished from an anaphylactic reaction as the therapy of the two conditions is entirely different. The presence of stridor is an important marker of laryngeal dystonia.

Risk factors for ADR include young age, male gender, a primary psychotic disorder, and prior drug-induced dystonic reactions. Patients with homozygous mutations in the CYPZD6 gene that results in slow DRBA drug metabolism are also at greater risk for ADRs [133]. Drug dosage does not seem to be a risk factor. Children have a greater risk for this adverse effect compared to adults. The incidence of ADR seems to be higher after administration of very potent DRBAs, such as haloperidol [132], but milder DRBA such as metoclopramide [134] and drugs with little effect on dopaminergic transmission, such as selective serotonin reuptake inhibitors [135], are also capable of inducing the same syndrome. Rare cases of ADR have been reported after administration of drugs that have no apparent dopamine blocking function, and patients with this syndrome exhibit the typical brisk response to anticholinergic therapy [136] discussed below. As an example of this phenomenon, both the antiviral drug foscarnet [137] and the commonly used antihistamine agent cetrizine [137] have been associated with ADR. ADR have also been reported with "ecstasy" (MDMA) use [138]. Although atypical antipsychotic agents have been associated with ADR [139], the incidence is lower than that associated with older neuroleptic agents [140, 141]. For example, a 25% incidence of ADR was reported in autistic children being treated with haloperidol [142], while a more recent trial of autistic children being treated with risperidone reported that none of 49 children developed ADR [141]. Cocaine used together with a DRBA predisposes to the development of ADR, and cocaine can cause ADR even when used alone [143]. Prophylactic pretreatment with anticholinergic drugs can reduce the incidence of ADR in susceptible individuals [132].

Children are not only at risk for ADR as a result of administration of prescribed DRBA, but also from secretive (parent's medication) or unwise (excessive dose) ingestion of these agents [144]. In one example, several teenagers and one younger child developed ADR after ingesting a medication they believed was "street Xanax," but actually contained haloperidol instead [145].

The treatment of ADR consists of administering intravenous diphenhydramine (25–50 mg) or benztropine (1–2 mg). Intravenous diazepam, a second-line therapy, is also usually effective. These therapies are extremely effective and the prompt benefit they produce helps confirm the diagnosis of ADR, and in the case of laryngospasm, may be lifesaving. After initial therapy of an ADR, it is wise to continue oral anticholinergic agents for 2 weeks, especially if a long-acting DRBA was used or in those cases where DRBA therapy must be continued. Premature discontinuance can result in recrudescence of symptoms [146]. Discontinuing anticholinergics should be done with a slow taper to avoid rebound worsening. Rarely, ADR can continue to recur over months despite discontinuance of the offending drug, requiring longer term anticholinergic therapy [147].

Dystonic Storm

Dystonic storm, also known as status dystonicus, is characterized by an acute onset of severe dystonic spasms or acute exacerbation of preexisting dystonia such that the patient is in extreme pain and/or at extreme risk for life-threatening complications. Dystonic storm can develop in patients with primary dystonia (e.g., DYT1 dystonia) or secondary dystonia (e.g., Batten's disease or cerebral palsy). Acute onset of dystonia can occur in the setting of initiation of a new drug (especially a dopamine blocking agent), withdrawal of

drugs in a dystonic patient (especially anticholinergic agents or intrathecal baclofen), or may simply be a severe spontaneous progression of a neurological condition for which dystonia is one possible clinical component (e.g., Wilson's disease). More commonly, dystonic storm is an event-related exacerbation of preexisting, generalized dystonia such as that associated with the DYT1 mutation. In patients with long-standing dystonia, an acute exacerbation may have an obvious precipitant, such as an intercurrent infection, recent trauma, or a change in medications. Alternatively, there may be no apparent cause for the sudden exacerbation of dystonia. The potential systemic complications of severe sustained dystonia are the main reason to consider this a medical emergency. Much like the systemic complications of NMS, patients experiencing dystonic storm can suffer respiratory embarrassment, rhabdomyolysis and myoglobinuria, potentially leading to renal failure [148]. Because of these potentially life-threatening developments, these patients are typically managed in an intensive care unit.

The circumstances that have precipitated dystonic storm in each individual patient are important to understand since they may dictate the therapeutic approach. Thus, dystonic storm related to intercurrent infection requires urgent initiation of appropriate antibacterial or antiviral therapy. Similarly, withdrawal of an offending medication or reinstitution of a precipitously withdrawn medication will prove to be the most important therapeutic step in other patients.

Once the precipitating circumstance has been identified and neutralized, therapy must be initiated to improve the dystonia itself and the systemic complications that have resulted from it. Medical therapy of dystonia may require any or a combination of dopamine-depleting agents (tetrabenazine), anticholinergic drugs (trihexyphenidyl), and/or dopamine blocking agent (haloperidol), each titrated to an effective or maximally tolerated safe dosage [148, 149]. Anticholinergic agents may be tolerated at higher dosages in those already receiving this class of medication and are also similarly well tolerated in high dosages by adolescents or young adults [150]. A variety of additional agents have been reported in individual cases to have provided benefit in cases of severe and acute dystonia, including dantrolene, baclofen, levodopa, carbamazepine, and various benzodiazepines. Intrathecal baclofen has been reported to be of benefit in a few patients refractory to medical therapy, but is not uniformly beneficial [151]. On the other hand, there are cases in which intrathecal baclofen was ultimately of benefit despite lack of efficacy of a test bolus prior to proceeding to an implantable pump [152]. Despite the most aggressive medical therapy, severe dystonic spasms may continue, raising the possibility that therapeutic paralysis, deep sedation, and ventilation may be required in an intensive care setting [153]. Deep sedation can be successfully achieved with propofol [154] or midazolam [155], both short-acting agents with the additional benefit of having gabaergic properties that might contribute to the antidystonic effect.

While in the intensive care unit, supportive measures will be required, including rehydration, control of fever, and careful monitoring of cardiac function and blood pressure. In patients, who are still uncontrolled after a period of paralysis, stereotactic surgery including pallidotomy or bilateral pallidal deep brain stimulation may ultimately be required [156, 157].

Stiff Person Syndrome

The stiff person syndrome (SPS) is associated with autoantibodies directed against glutamic acid decarboxylase (GAD). Although there is controversy about the role of these antibodies, they presumably act by reducing GABA-mediated inhibition of spinal interneurons with resultant axial and limb rigidity [158]. GAD antibodies are also found in patients with type 1 diabetes, but typically at much lower titers. The clinical syndrome consists of profound rigidity of predominantly axial and proximal limb muscles with superimposed, often stimulus sensitive, muscle spasms that can be severe enough to produce long bone fractures. These spasms, and the ongoing rigidity, can occasionally be life threatening, in

that they can result in respiratory embarrassment, autonomic dysfunction, or both [159]. The clinician should be aware that any combination of one, two or three, or all four limbs can be involved separately, giving rise to a variant of the condition termed "stiff limb" syndrome [160].

There is also a paraneoplastic form of SPS, related to antiamphiphysin antibodies. Unlike ordinary SPS which has a male predominance, the paraneoplastic form, most common in breast cancer, has a female predominance. In SPS the legs and axial muscles, especially the lower paraspinal muscles, are most commonly affected, whereas in amphiphysin antibody SPS, the arms and neck muscles are often most prominently affected [161]. A still more serious, although rarer form, is progressive encephalomyelitis with rigidity and myoclonus (PERM). The autoimmune form of SPS is associated with a high incidence of other autoimmune conditions, such as thyroiditis and systemic lupus, and in fact may be the initial manifestation of a systemic autoimmune condition such as lupus [162]. Similarly, paraneoplastic SPS can be the presenting symptoms of an occult carcinoma [163]. The clinician who is unfamiliar with this syndrome can easily conclude that a patient with SPS is hysterical, as sensory, long tract, cognitive, and coordination findings are typically absent [164], and on occasion, only one, two, or three limbs are affected.

Symptomatic therapy of the rigidity in this condition consists of administration of gabaergic agents, such as clonazepam, diazepam, and baclofen. A variety of antiepileptic drugs, including vigabatrin, tiagabine, gabapentin, and levetiracetam, are considered to be somewhat beneficial [165]. Treatment of the underlying autoimmune condition can be carried out with IVIg [166], corticosteroids [167], and, as recently demonstrated, rituximab [168]. IVIG is the best studied immunosuppressive therapy and is generally considered the preferred agent in this category [164]. Although immunosuppressive therapy may be effective, it cannot be expected to have an immediate effect in an emergency room setting. Intrathecal baclofen can result in more rapid clinical improvement [169], but paradoxically any dysfunction in the baclofen pump system, such as pump failure or catheter leakage, can cause a baclofen withdrawal syndrome with an even more severe exacerbation of rigidity [170], making it imperative that both the clinician and the patient be aware of this possibility. Recently, the GABA receptor potentiator, propofol, in modest intravenous dosages, has been used with significant benefit to provide immediate relief of SPS spasms without attendant sedation [171]. In this circumstance it can be used as a therapeutic bridge pending the placement of a baclofen pump or until potent immunotherapy takes effect.

Hemiballism and Hemichorea

Large amplitude, proximally predominant flinging movements are characteristic of ballism. These movements are thought to exist on a clinical continuum with the smaller amplitude, more distally predominant movements of chorea. The fact that these two different types of abnormal involuntary movements are pathophysiologically related is supported by the observation that both may exist in the same individual at the same time, and ballism, as it improves, may evolve into chorea. In those cases in which chorea and ballism coexist or the abnormal movement is in an indeterminate zone between the two, the term hemichorea/hemiballism is often used. Ballistic movements are anatomically classified as monoballism (involving one limb), hemiballism (involving one side of the body), biballism (involvement of both side of the body), or paraballism (involvement of both lower extremities). In those cases in which hemiballism is due to involvement of the STN, the somatotopic organization of this structure may account for the selective involvement of only one limb on one side of the body [172], and the same could be said of patients with a cortical lesion. Although the STN is a common location of structural pathology associated with hemiballism, modern neuroimaging has proven that it may not be the structure involved in the majority of cases. Other structures in the STN afferent or efferent pathways such as the striatum, thalamus, globus pallidus, and cerebral cortex may also be the locus of pathology [173]. In one of the largest

series in the literature with poststroke hemichorea/hemiballism, only four of 27 patients had lesions confined to the STN, while six each were in the stratum or cortex, with other isolated lesions being found in the putamen, caudate, or globus pallidus [173].

Ischemic and hemorrhagic strokes are the most common causes of hemiballism. In some cases of apparent vascular hemiballism, neuroimaging is totally normal, and in others, the CT scan result is normal but MRI reveals a lacunar infarction in the STN or elsewhere [174]. Hemichorea/hemiballism develops on the day of stroke onset in the vast majority of cases, but in up to 10% it may develop a day later, and in rare cases as long as 5 days later [173]. Vascular hemichorea can also appear in the form of a TIA, so-called limb-shaking TIAs [175]. Although the prognosis for survival in those with vascular hemiballism was once thought to be worse than other stroke patients, especially in the preneuroleptic era, recent studies suggest that vascular hemiballism patients, many of whom have had lacunar strokes, have a risk of stroke recurrence and death that is similar to stroke patients in general [176]. As in the case with other stroke syndromes, surgical or neurointerventional procedures that improve cerebral circulation may have a salutary effect on vascular hemiballism [177], as discussed below.

A variety of other pathologies including encephalitis, systemic lupus erythematosus, multiple sclerosis, basal ganglia calcification, and nonketotic hyperglycemia can also result in hemiballism [178]. Structural pathologies such as bacterial or tuberculosis abscess, neoplasm, moyamoya disease, HIV-related toxoplasmosis, or arteriovenous malformation have also been associated with hemiballism. Stereotactic ablation of the STN for the treatment of Parkinson's disease can result in hemiballistic movements that are transient and improve in a matter of weeks [179], but can also rarely result in permanent hemiballism [180]. Similarly, therapeutic stimulation of the STN for Parkinson's disease can produce hemiballism that resolves when the stimulation is adjusted below a given threshold voltage [181].

The syndrome of hemiballism–hemichorea and magnetic resonance striatal hyperintensity associated with nonketotic hyperglycemia has been reported increasingly more frequently in recent years [182] and now represents the second most common cause of hemiballism, stroke being the most common. This syndrome appears to be much more common in patients of Asian descent [182]. In these cases, CT scan of the brain typically reveals hyperintensity in the contralateral striatum corresponding to MRI scans that show increased signal intensity on T1-weighted images and a decreased signal on T2-weighted scans. A high signal is occasionally seen on diffusion-weighted imaging [183]. After metabolic correction of the hyperglycemic state, the abnormal involuntary movement usually disappears along with the CT and MRI abnormalities. In some cases, however, hemiballism persists despite disappearance of the MRI abnormality [184, 185]. Interestingly, the same CT and MRI findings have been seen in some hyperglycemic patients with no involuntary movements [186]. The exact nature of the striatal pathology remains unclear. The finding of normal gradient-echo MR images in hyperglycemic hemiballism along with striatal high signal intensity on a diffusion-weighted scan has suggested to some authors that hyperviscosity with associated cytotoxic edema may play a role in this syndrome [183]. However, autopsy and biopsy evaluation of the striatal tissue demonstrating MRI hyperintensity has revealed evidence of multiple foci of recent infarcts and/or gliosis [187, 188]. PET scans performed in the acute and subacute phases have suggested glucose hypometabolism in the affected regions of the brain [189].

The first therapeutic measure in treating hemiballism is to correct the underlying metabolic, infectious, or vascular abnormality to the extent possible. In the circumstance of nonketotic hyperglycemia and ischemic stroke, the two most common causes of hemiballism, this means correcting the hyperglycemia in the former condition, and reversing the ischemia in the second condition through methods such as supporting blood pressure, thrombolytic therapy, and endovascular procedures. Acutely reversing ischemia will have little effect on hemiballism due to a completed stroke, but can be effective when the abnormal movements are related to transient

ischemia [175, 177]. Hemiballism related to hyperglycemia may reverse within hours of correcting the metabolic abnormality, but up to 20% of patients continue to have ballism for months. Vascular hemiballism due to a completed stroke improves spontaneously in the majority of patients. In a series of 25 such patients followed for up to 3 years, hemiballism completely disappeared in 56% of cases after a mean duration of 15 days [173]. In another series of the same size, full recovery was noted after 3–15 days in 56% of patients [176].

In the absence of spontaneous or therapeutic reversal of hemiballism, it must then be treated symptomatically. For control of the abnormal involuntary movement itself, DA blocking or depleting drugs are the most effective symptomatic therapy. Traditionally, typical neuroleptics such as haloperidol have been used for this purpose, but more recently low-dose clozapine, olanzapine, and other atypical antipsychotic agents have also been found to be effective [190, 191]. The DA-depleting drugs reserpine [192] and tetrabenazine [193] can improve ballism. Caution must be exercised with either of these two agents not to induce hypotension in stroke patients. Anticonvulsants are occasionally beneficial, including valproic acid [194], topiramate [195], and levetiracetam [196]. Sertraline (Zoloft) has been reported to result in a prompt and nearly complete improvement of hemiballism in a single case [197]. In vascular hemichorea, physical therapy may speed improvement in the movement disorder [198]. If all these therapies fail and the amplitude of ballism threatens to produce physical injury, extreme exhaustion, or cardiac symptoms, stereotactic surgeries consisting of contralateral thalamotomy [199], pallidotomy [200], or thalamic deep brain stimulation [201] have all been shown to be useful therapies.

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Encephalopathy

15

Steven L. Lewis

Abstract

The term encephalopathy describes a general alteration in brain function manifesting as an attentional disorder anywhere within the continuum between a hyperalert agitated state and coma, and typically refers to the commonly encountered clinical scenario of diffuse brain dysfunction felt to be due to a systemic, metabolic, or toxic derangement. This chapter discusses an approach to the emergency evaluation and management of patients with encephalopathy, with an emphasis on those causes of toxic-metabolic encephalopathy that will lead to irreversible neurological dysfunction if not recognized and treated urgently, as well as those encephalopathies whose recognition might lead to more prompt diagnosis and treatment of the causative medical illness.

The encephalopathies discussed in this chapter are divided into four common, though overlapping, scenarios the neurologist is likely to encounter in clinical practice: encephalopathy from metabolic disorder or deficiency, encephalopathy due to a severe systemic illness or organ failure, encephalopathy due to medication-related toxicity, and encephalopathies diagnosable primarily by findings on brain imaging. In many cases a specific etiological diagnosis can be made—via history, examination, laboratory studies, and in some cases, imaging—which may lead to specific medical intervention and more rapid clinical resolution, and may help prevent irreversible neurologic dysfunction.

Since patients with diffuse, toxic-metabolic encephalopathies are medically—and secondarily neurologically—ill, the evaluation and management of patients with diffuse encephalopathies represents a unique and important opportunity for the neurologist to positively impact the medical management, and both the neurological and medical recovery, of these systemically ill patients.

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Introduction

Encephalopathy is the term used to describe a general alteration in brain function, manifesting as an attentional disorder anywhere within the continuum between a hyperalert agitated state and coma. In clinical practice, the diagnosis of encephalopathy is usually reserved for the diffuse brain dysfunction felt to be due to a systemic, metabolic, or toxic derangement, rather than, for example, a multifocal structural process; therefore the adjectives "metabolic" or "toxic-metabolic" are usually implied when the diagnosis of encephalopathy is made. The syndrome of toxic-metabolic encephalopathy is essentially synonymous with *delirium*, the term favored by most nonneurologists. Lately, *autoimmune* encephalopathies have been increasingly recognized as another important mechanism of diffuse brain dysfunction; these syndromes—technically more consistent with "encephalitides" than "encephalopathies"—are characterized by suggestive clinical and laboratory features and response to immune-based therapies (and often removal of an underlying neoplasm), distinguishing them from the toxic-metabolic encephalopathies discussed in this chapter.

Neurologists are frequently asked to evaluate patients with alteration in consciousness from a toxic-metabolic encephalopathy. The consulting physician likely requests the neurologic consultation because of concern for a structural, ischemic, epileptic, or other focal cause of the patient's encephalopathic symptoms. The neurologic diagnosis of a diffuse, toxic-metabolic encephalopathy is typically made by finding characteristic diffuse clinical symptoms and (mostly) nonlocalizing findings within the appropriate clinical context, usually with exclusion of other processes through imaging and other studies. The diagnosis of toxic-metabolic encephalopathy may lead to the generic recommendation to correct any metabolic abnormalities, treat any underlying acute systemic illness, and discontinue or limit the use of sedatives or other medications with central nervous system side effects. In many cases, though, a more specific diagnosis can be made, and prompt recognition of the causative systemic process or medication can lead to a more rapid neurologic recovery, or in some cases, prevention of irreversible neurologic injury [1].

The purpose of this chapter is to discuss an approach to the emergency evaluation of patients with encephalopathy, with an emphasis on those causes of toxic-metabolic encephalopathy that will lead to irreversible neurological dysfunction if not recognized and treated urgently, as well as the encephalopathies whose recognition (by clinical or neuroimaging findings) might lead to more prompt diagnosis and treatment of the causative medical illness.

Epidemiology of Toxic-Metabolic Encephalopathy

The evaluation of encephalopathy is a common aspect of day-to-day neurologic practice, and encephalopathy can occur in any patient at any age with a severe systemic illness or with exposure to a metabolic or toxic derangement causing cerebral dysfunction. The epidemiology of toxic-metabolic encephalopathy, however, is best characterized for those patients over age 65, where the incidence of delirium occurring during hospitalization in this age group has been reported to be as high as 56% (up to 87% in the ICU setting)

with high in-hospital mortality (varying between studies), and with a 1-year mortality rate of up to 40% [2]. These statistics underscore both the ubiquity of this clinical syndrome and the fact that encephalopathies are usually reflective of severe underlying acute systemic disease or dysfunction.

Pathophysiology of Toxic-Metabolic Encephalopathy

A detailed discussion of the underlying pathophysiology of each of the many causes of toxic-metabolic encephalopathy is outside the scope of this chapter. However, among the many mechanisms of global neuronal and astrocytic dysfunction that can occur due to metabolic or toxic derangements, general pathophysiologic mechanisms that underlie many of these clinical syndromes include creation of an energy deficit through a decrease in the level of basic metabolic substrates necessary for neuronal survival, oxidative stress, and functional alterations of neurotransmitter systems, including alterations in neurotransmitter synthesis and release [3].

From an emergency management perspective, with brain survival as the primary goal, those pathophysiologic causes of metabolic encephalopathy that may directly result in cell death due to loss of neuronal energy substrates (e.g., glucose, oxygen, and thiamine) are particularly critical to recognize and immediately treat in order to prevent irreversible neuronal death, and to increase the likelihood of clinical neurologic recovery. Also critical to immediately recognize are those systemic processes that can *secondarily* cause irreversible neuronal injury, for example, by causing increased intracranial pressure (ICP) and potential cerebral herniation (e.g., acute hepatic encephalopathy from fulminant hepatic dysfunction). On the other hand, all causes of toxic-metabolic encephalopathy share the underlying pathophysiology of (usually severe and often life-threatening) systemic illness and dysfunction, underscoring the importance of accurate diagnosis and treatment no matter what the underlying systemic process.

Although the basic underlying cellular pathophysiology of metabolic encephalopathies may differ, they share a common mechanism of generalized, rather than focal, alteration in cortical and brainstem function, leading clinically to a diffuse alteration in attention and arousal. Some encephalopathic syndromes, however, preferentially affect certain vulnerable brain regions specific to the cause of the encephalopathy, such as the medial thalami and periaqueductal gray matter in thiamine deficiency.

Clinical Features of Toxic-Metabolic Encephalopathy

Patients with toxic-metabolic encephalopathy typically present with a global alteration in level of alertness, varying between and within patients, from obtundation and coma to an agitated delirium. The time course of development of the encephalopathy can vary from rapid (e.g., from acute hypoglycemia, hypoxia, or drug overdose), to the more common subacute presentation from insidiously developing systemic metabolic processes.

On clinical examination, patients with encephalopathy are often lethargic, confused, or agitated, typically without obvious focal localizing neurologic features. Many patients with toxic-metabolic encephalopathies exhibit *asterixis*, elicited by asking the patient to hold his or her arms outstretched. Asterixis is manifested by a very brief loss of postural tone of the outstretched arms. It is not necessary for the wrists to be dorsiflexed to evaluate for asterixis; however, if the patient is able to perform this, the classic "flap" of brief downward wrist flexion may be observed. The finding of bilateral asterixis is rather specific (but not sensitive) for the presence of a toxic-metabolic encephalopathy from a number of potential processes, but is not suggestive of any particular cause of the encephalopathy. In clinical practice, though, asterixis is commonly associated with uremic or hepatic encephalopathies.

Although the hallmark of the toxic-metabolic encephalopathies is disordered attention, seizures can occur in some syndromes as well, particularly when severe; these include disorders such as

hypoglycemia and hyperglycemia, some electrolyte disorders, acute hepatic failure, and various medication-related encephalopathies (see the section on "Encephalopathic Syndromes" below).

Diagnosis of Toxic-Metabolic Encephalopathy

As when taking any neurologic history, the physician should delineate the clinical symptoms and their time course (especially from witnesses if the patient is unable to provide a history), carefully detailing the current systemic context, other medical comorbidities, and all current and recent medications. Examination should focus not only on the generalized neurologic findings expected in a diffuse encephalopathy, including assessment for asterixis, but should also focus on assessing vital signs, signs of meningeal irritation, observation for aphasia (especially the fluent kind, as a mimic of a confusional state), funduscopic examination for signs of increased intracranial pressure, and exclusion of obvious motor or other asymmetries for which an alternative diagnosis may be more likely.

Despite the diffuse neurologic presentation of patients with a probable toxic-metabolic encephalopathy, diagnostic evaluation often necessitates brain imaging studies (CT or MRI) to rule out causative focal structural or ischemic lesions, especially if there is any uncertainty as to the diagnosis. Although these imaging studies are typically performed specifically to exclude focal structural or ischemic processes, and should therefore typically be unrevealing in the patient ultimately diagnosed with a diffuse encephalopathy, some toxic-metabolic processes are themselves associated with abnormal imaging features that may be helpful in diagnosis [4] and are discussed further in the section on "Encephalopathic Syndromes" below.

EEG can be helpful in the evaluation of the patient with encephalopathy, particularly when subclinical status epilepticus is a diagnostic consideration. Diffuse slowing on the EEG is a nonspecific, and a nearly ubiquitous finding in these patients, simply paralleling the clinical syndrome of a diffuse cerebral process. The EEG finding of triphasic waves is rather specific, but not sensitive, for a toxic-metabolic encephalopathic process, but is not specific as to the actual cause; however, like asterixis, in clinical practice this finding is often encountered with hepatic and uremic encephalopathies.

Laboratory testing is the mainstay of investigation of the etiology of toxic-metabolic encephalopathy. Serum glucose testing (including rapid finger stick determination as well as laboratory analysis of a drawn blood sample) and pulse oximetry should be immediately assessed in all patients because of the potentially irreversible nature of hypoglycemic and hypoxic encephalopathy unless rapidly diagnosed and treated. A complete metabolic profile (including electrolytes and liver and kidney function tests) will quickly assess for the most common metabolic and systemic derangements, and a complete blood count will quickly exclude profound anemia, while also looking for clues to an underlying infectious process.

Lumbar puncture (LP) will show only nonspecific, if any, cerebrospinal fluid abnormalities in a patient with a toxic-metabolic encephalopathy; however, this should be performed when there is any clinical concern for meningoencephalitis (including autoimmune encephalitis) or subarachnoid hemorrhage. Lumbar puncture in the encephalopathic patient typically should be performed only after screening neuroimaging has excluded a focal cerebral mass lesion which might contraindicate this procedure.

Encephalopathic Syndromes

Patients with diffuse toxic-metabolic encephalopathies are medically, and secondarily neurologically, ill. Therefore, despite the ubiquity of these clinical syndromes in typical inpatient neurological consultative practice, evaluation of patients with diffuse encephalopathies represents a unique and important opportunity for the neurologist to positively impact the medical management, and both the neurological and medical recovery, of these systemically ill patients.

This section outlines four common and distinct (but overlapping) presentations the physician is likely to encounter in clinical practice: encephalopathy from metabolic disorder or deficiency, encephalopathy due to a severe systemic illness or organ failure, encephalopathy due to medication-related toxicity, and encephalopathies diagnosable primarily by findings on brain imaging.

Encephalopathy from Basic Metabolic Disorder or Deficiency

Oxygen, Glucose, and Electrolytes

As stated above, hypoxemia and hypoglycemia are critical to consider and quickly exclude in any encephalopathic patient, as deficiencies of these basic and critical neuronal energy substrates will lead to irreversible neuronal death unless recognized and reversed quickly; most other metabolic disorders are less likely to directly lead (or lead quickly) to neuronal cell death and irreversible injury. Likewise, profound hypotension or anemia can lead to loss of energy supply to neurons and should be excluded quickly via immediate assessment of vital signs, oxygen saturation, and hemoglobin concentration; careful therapeutic attention should be placed on these basic emergency resuscitation parameters in all encephalopathic patients, as in any critically ill patient.

In addition to hypoxemia and hypoglycemia, encephalopathy frequently occurs in the setting of hyperglycemia and of certain electrolyte abnormalities, especially hyponatremia, hypernatremia, and hypercalcemia. Though hyperkalemia and hypokalemia are well-known causes of neuromuscular dysfunction (and of cardiac dysfunction which can secondarily cause hypoxic-ischemic encephalopathy), these common potassium abnormalities are not typically associated with encephalopathy.

Thiamine Deficiency (Wernicke's Encephalopathy)

Thiamine, in the form of its active phosphorylated derivatives (especially thiamine diphosphate, also called thiamine pyrophosphate), is an important coenzyme in a number of intracellular enzymatic activities, including energy production and various biosynthetic pathways. Deficiency of thiamine causes Wernicke's encephalopathy, characterized classically by the clinical triad of ophthalmoplegia, mental status changes, and ataxia. This is a very important cause of encephalopathy due to the potential irreversibility of clinical findings, and especially because of the development of an irreversible amnestic state, if thiamine deficiency is not recognized and treated emergently [5, 6]. Although commonly thought of as a disease of alcoholics, Wernicke's encephalopathy can occur due to any process that leads to inadequate absorption of thiamine, including hyperemesis states such as hyperemesis gravidarum, malnutrition from any cause, bariatric surgery, chronic diarrheal illnesses, and in the course of many systemic illnesses [6, 7].

Despite the commonly memorized clinical triad, the clinical symptoms and signs in patients with Wernicke's encephalopathy vary, and the full triad is often not present in an individual patient. The most common symptom is mental status change, manifesting as agitation and confusion or apathy, and can progress to coma. Eye findings, if present, most commonly include nystagmus and sometimes sixth nerve palsies; complete "ophthalmoplegia," as listed in the classic triad, is actually rare. Ataxia of gait is often present. Other signs and symptoms that may be seen in patients with Wernicke's encephalopathy include hypothermia, hypotension, and tachycardia [6].

Brain regions commonly involved in Wernicke's encephalopathy include the mamillary bodies, periaqueductal gray matter, and medial thalami; changes in these regions may be seen on diffusion-weighted and T2-weighted MRI in some patients with Wernicke's encephalopathy. These particularly vulnerable brain regions explain the characteristically severe, and potentially irreversible, amnestic state (Korsakoff's syndrome) that occurs in patients with Wernicke's disease if prompt treatment is not initiated.

Because of the treatable aspect of this condition, and its neurological irreversibility if untreated in a timely fashion, neurologists need to keep this diagnosis in mind in all patients

presenting with encephalopathy, whether or not other features of the syndrome (e.g., nystagmus or gait ataxia) are present. The diagnosis is primarily and typically entirely clinical; thiamine levels are not useful in practice, especially due to delay in obtaining these results. Although MRI findings can be seen in some patients with Wernicke's encephalopathy, these findings are insensitive for the diagnosis; importantly, one of the priorities is to try to make the clinical diagnosis and begin treatment *prior to* the development of any imaging findings.

Treatment with parenteral thiamine should be initiated emergently in any patient in whom the diagnosis is a reasonable consideration, and must be given prior to any glucose administration due to the risk of glucose precipitating or worsening Wernicke's encephalopathy. Although the optimal evidence-based dose of thiamine is uncertain, recent expert recommendations suggest that initial parenteral thiamine dosing should be >500 mg daily, given as a once- or twice-daily regimen, for 3–5 days [6, 8].

Encephalopathy Due to Severe Systemic Illness or Organ Failure

Severe Systemic Illness and Septic Encephalopathy

As discussed in the preceding sections (and to a great extent inherent in the diagnosis of the clinical syndrome of a toxic-metabolic encephalopathy) encephalopathies commonly occur in the setting of a severe underlying systemic illness. Encephalopathy is especially common in patients in the medical ICU [9, 10], and in patients whose illness may be severe enough to warrant transfer to a medical ICU setting. Any medical illness of sufficient severity can lead to the clinical syndrome of a toxic-metabolic encephalopathy; in addition, the common finding of encephalopathy in the specific clinical setting of systemic sepsis, with or without multiorgan failure, has led to the designation of a *septic encephalopathy* [11]. The pathophysiology of septic encephalopathy is unclear, although theoretical mechanisms include the effects of inflammatory mediators, blood–brain barrier dysfunction, and other possible metabolic effects of the severe systemic dysfunction [11].

Although sepsis or severe acute medical illnesses of any cause are common etiologies of encephalopathy, encephalopathies also occur due to single-organ dysfunction or failure. In each of these clinical scenarios, the neurologist can play an important role in helping to pinpoint the causative medical illness, which may have a direct impact on systemic treatment and the course of neurologic improvement. The specific single-organ causes of encephalopathy discussed below include hepatic encephalopathy, uremic encephalopathy, pancreatic encephalopathy, and the fat embolus syndrome.

Hepatic Encephalopathy

Hepatic encephalopathy can occur in patients with either chronic liver disease (cirrhosis) or acute liver failure [12]. Encephalopathy due to *chronic* liver disease typically progresses slowly, with the clinical features defined in stages, or grades; minimal hepatic encephalopathy is characterized by subtle findings detectable mainly by formal neuropsychological testing: grade I is characterized by psychomotor slowing and lack of attention; grade II is characterized by disorientation, lethargy, and unusual behavior; grade III is characterized by somnolence and stupor; and patients in grade IV hepatic encephalopathy are in coma.

Asterixis is most commonly associated with grade II hepatic encephalopathy, but can also be seen in other stages. Some patients with chronic liver disease present as a slowly progressive parkinsonian syndrome (sometimes called acquired (non-Wilsonian) hepatolenticular (or hepatocerebral) degeneration) consisting of bradykinesia, rigidity, tremor, dysarthria, and ataxia [13]. Seizures are uncommon in patients with hepatic encephalopathy due to chronic liver disease.

The diagnosis of hepatic encephalopathy due to cirrhosis is made by observing the characteristic neurologic clinical features in the appropriate clinical context. Ammonia levels remain helpful in the clinical diagnosis of hepatic encephalopathy, although these levels do not correlate well with the various stages of encephalopathy, and a

normal serum ammonia level does not exclude the diagnosis of hepatic encephalopathy. As mentioned in the section on "Diagnosis" (above), triphasic waves may be seen on EEG in some patients with hepatic encephalopathy, but this finding is neither sensitive nor specific for hepatic encephalopathy.

The MRI finding of high signal in the bilateral globus pallidus on noncontrast T1-weighted images has been attributed to manganese deposition in the brain due to reduced biliary manganese excretion; this MRI finding, however, is common in patients with chronic liver disease, whether or not a clinical encephalopathy is present [13].

Treatment of hepatic encephalopathy is aimed at reducing ammonia production through the use of antibiotics such as rifaximin, and reducing ammonia absorption through the use of nonabsorbable disaccharides, such as lactulose. A recent double-blind, placebo-controlled trial of rifaximin in hepatic encephalopathy showed that rifaximin-treated patients had an approximately 50% reduction in episodes of hepatic encephalopathy and hepatic encephalopathy-related hospitalizations; many of the patients in this study received concomitant lactulose therapy, attesting to the common clinical requirement for both modes of therapy [14]. Rifaximin was approved by the US Food and Drug Administration for the treatment of hepatic encephalopathy in March 2010.

In contrast to patients with chronic cirrhosis and portosystemic shunting, *acute* liver failure commonly presents as rapidly progressive neurologic deterioration leading to life-threatening cerebral edema, with coma and seizures [15]. The neurologic assessment and treatment of patients with acute hepatic encephalopathy consist of ICP monitoring with aggressive reduction of increased ICP and management of any associated seizures.

Uremic Encephalopathy

Encephalopathy can occur due to either acute or chronic renal failure, and typically develops more rapidly in patients with acute kidney dysfunction [16]. Symptoms of uremic encephalopathy include asterixis, myoclonus (uremic twitching), and coarse tremor; seizures may also be seen. The clinical symptoms and signs, including the EEG finding of triphasic waves in severe uremic encephalopathy, mimic those of many other metabolic encephalopathies; however, the tremulousness and twitching seen in many patients with uremic encephalopathy, although not very specific, may be somewhat more suggestive of this cause of encephalopathy compared to other systemic processes.

The diagnosis of uremic encephalopathy is clinical, supported by appropriate laboratory studies showing severe kidney dysfunction, along with the reasonable exclusion of other potentially causative systemic, or other, processes. Other systemic causes of encephalopathy that especially need to be considered in the uremic patient include drug toxicities (especially those that are renally metabolized or excreted), electrolyte disturbances, and thiamine deficiency [17]. Treatment of uremic encephalopathy is based on improvement of the uremic state and appropriate adjustment, if possible, of renally metabolized/excreted medications.

Pancreatic Encephalopathy

The term "pancreatic encephalopathy" was coined in 1941 to describe the known association between acute pancreatitis and a severe diffuse encephalopathy [18]. Since then a number of reports have further elucidated this syndrome [19–21] which we have recently reviewed [1]. Pancreatic encephalopathy typically has been reported to occur within 2 weeks of pancreatitis onset, especially between the second and fifth days, with varying incidences (up to as high as 35%) reported [1].

The diagnosis of pancreatic encephalopathy should be considered in any patient with a diffuse encephalopathy occurring in the setting of acute pancreatitis. Other than the laboratory findings diagnostic of pancreatitis, no specific laboratory or imaging feature is diagnostic of pancreatic encephalopathy; however, one report described severe diffuse white matter abnormalities on MRI in a patient with this syndrome [22].

Treatment consists solely of management of the pancreatitis; there is no specific neurologic treatment beyond supportive care and avoidance

of benzodiazepines, which may worsen the encephalopathy. Neurologic improvement typically parallels the patient's systemic recovery. Unfortunately, the mortality rate for patients with pancreatic encephalopathy is high [1].

The pathogenesis of pancreatic encephalopathy has been proposed to relate to blood–brain barrier breakdown as a consequence of activation of phospholipase A and conversion of lecithin into its hemolytic form [19], although fat embolism (see below) is another putative mechanism. Patients with pancreatitis are also at risk for the development of Wernicke's encephalopathy, which should strongly be considered in the differential diagnosis, or as an additional comorbid process, in these patients [23].

Fat Embolism

Fat embolism should be considered among the potential emergent diagnoses of any patient presenting with a diffuse encephalopathy in characteristic clinical settings, such as after recent orthopedic procedures or trauma. The fat embolism syndrome is characterized by the classic clinical triad of encephalopathy, pulmonary dysfunction, and a petechial rash [24]. Although most commonly associated with long-bone trauma, fat embolism also occurs in a variety of other scenarios, including acute pancreatitis, diabetes mellitus, burns, joint reconstruction, liposuction, cardiopulmonary bypass, decompression sickness, and parenteral lipid infusion [25]. Clinical symptoms of fat embolism typically, though not invariably, occur 24–48 h after the inciting event [24].

The primary neurologic manifestation of fat embolism is a diffuse encephalopathy, though focal neurologic signs and seizures can occur. In some patients, the neurologic manifestations may be the sole clinical feature; however, pulmonary symptoms are typically present and these symptoms may range from mild dyspnea to tachypnea to respiratory failure [26]. The finding of petechiae on the skin completes the clinical triad, but this is seen in only about half of patients with the syndrome. MRI in some patients has shown multifocal punctate DWI-positive white matter lesions consistent with multifocal embolic lesions [27, 28].

Two major mechanisms have been proposed to explain fat embolism syndrome. The mechanical theory proposes that bone marrow contents enter the lungs via the venous system, where they may also gain access to the systemic circulation and enter the brain via pulmonary arteriovenous shunts or patent foramen ovale. The biochemical theory proposes that pulmonary abnormalities result from a toxic effect on lung cells by circulating free fatty acids. These theories are not mutually exclusive and both mechanisms may be responsible for various aspects of the clinical syndrome [25].

The possibility of fat embolism should be considered in any patient with encephalopathy occurring in the appropriate clinical context, especially if other causes have been excluded. Treatment is currently supportive and revolves mainly around appropriate pulmonary management [24].

Medication-Related Encephalopathy

Encephalopathy due to medications with central nervous system effects, including sedatives, analgesics, anticholinergics, anticonvulsants, anxiolytics, and any of the wide variety of CNS-active drugs, is well recognized. However, several medications in current clinical use have been relatively recently associated with specific and distinctive toxic encephalopathic syndromes and will be discussed here. These medications, ifosfamide and cefepime, are not uncommonly used and neurologists in clinical practice are likely to be asked to consult emergently on patients with encephalopathy due to one of these agents. Recognition of these unusual encephalopathic syndromes is important in the management of these patients to avoid unnecessary interventions (other than discontinuation or reduction of the offending agent) and possibly (in the case of ifosfamide encephalopathy) for consideration of specific antidotal therapy. Metronidazole, a commonly used antibiotic which is also associated with an encephalopathic syndrome, is discussed in the next section on encephalopathies associated with distinctive imaging findings.

Ifosfamide

Ifosfamide, a chemotherapeutic agent used in the treatment of a variety of solid tumors, has been associated in some patients with the development of a severe encephalopathy [29]. Ifosfamide encephalopathy typically develops 24–48 h after infusion, but may occur later. Encephalopathic symptoms due to ifosfamide may range from mild to severe and progress to coma and death. In addition, a distinctive catatonic-like, severely abulic state with mutism can be seen in patients with ifosfamide encephalopathy [30].

Due to theoretical considerations regarding the presumptive mechanism of ifosfamide encephalopathy, methylene blue, an electron acceptor, has emerged as antidotal intravenous treatment of severe cases of this syndrome [31, 32]. Although not based on controlled trials, treatment with methylene blue has been generally thought to hasten what may otherwise be a prolonged recovery with occasional persistent neurologic sequelae [33]. Mild cases, however, typically resolve within days after stopping the agent and do not require specific antidotal treatment. Thiamine treatment has also been anecdotally advocated for management of this syndrome [34]. A recent uncontrolled retrospective analysis, however, suggested no clear benefit for routine prophylaxis of ifosfamide encephalopathy with methylene blue or thiamine [35].

Cefepime

Cefepime is a fourth-generation cephalosporin commonly used to treat a variety of severe bacterial infections. This agent has been associated with an encephalopathy (more common than that associated with third-generation cephalosporins, such as ceftriaxone and ceftazidime), manifested by progressive confusion and agitation which can progress to coma [36, 37]. Although cefepime encephalopathy was initially reported in patients with renal failure (causing reduced clearance of the drug), cefepime encephalopathy also occurs in patients with normal renal function [38, 39]. In some patients with cefepime encephalopathy, EEG has shown nonconvulsive status epilepticus [39–41].

Management involves discontinuation of cefepime, which leads to gradual resolution of the encephalopathy. In patients with nonconvulsive status epilepticus due to cefepime (or other cephalosporin) neurotoxicity, several reports have described short-term use of anticonvulsants in addition to discontinuation of the cephalosporin [40, 41], although it is unclear as to whether improvement was aided by the anticonvulsant.

Encephalopathies Diagnosed Primarily by Brain Imaging Findings

Findings on neuroimaging play an integral role in the timely recognition of several specific encephalopathic conditions, including the posterior reversible encephalopathy syndrome and metronidazole encephalopathy; in addition, the finding of a splenial lesion on MRI, although nonspecific, has been recently associated with various causes of encephalopathy. The imaging findings and clinical syndromes discussed in this section are in contrast with some of the encephalopathic syndromes discussed earlier, where the imaging findings are not specific or sensitive for the clinical presence of an encephalopathy (e.g., T1 high signal in the basal ganglia in patients with chronic hepatic disease with or without encephalopathy) or they represent late findings that play little if any role in clinical diagnosis and emergent empiric therapy (e.g., the MRI findings in Wernicke's encephalopathy).

Posterior Reversible Encephalopathy Syndrome

This is an increasingly recognized clinical syndrome, although controversially named since it does not always involve posterior brain regions and is not always completely reversible. The posterior reversible encephalopathy syndrome typically presents clinically with encephalopathy, visual disturbances (due to cortical visual dysfunction), and seizures, usually in association with elevated systemic blood pressure. The classic imaging finding is hyperintensity on T2- and FLAIR-weighted MRI consistent with vasogenic

edema, typically predominantly involving the posterior occipital white matter; however, more diffuse involvement (including the brainstem and anterior hemispheres) can also be seen [42]. The predisposing conditions for the development of this syndrome are vast, although common underlying systemic factors include eclampsia, hypertension with acute kidney disease, and exposure to various chemotherapeutic and immunosuppressive medications. The cause of the posterior reversible encephalopathy syndrome is unclear, but may involve capillary leak due to endothelial dysfunction. Treatment includes blood pressure control, withdrawal of the potentially offending agent, and seizure management. It is assumed that prompt recognition and management of this syndrome should decrease the likelihood of permanent sequelae of this usually reversible condition [43].

Metronidazole Encephalopathy

Metronidazole is a commonly prescribed antibiotic which is associated with an uncommon, but characteristic, toxic encephalopathy manifested primarily by confusion, dysarthria, and ataxia. MRI findings typical of metronidazole encephalopathy include T2 and FLAIR high-signal lesions involving the dentate nuclei [44]; additional involvement of the corpus callosum and deep hemispheric white matter, and hypertrophy of the inferior olives have also been described [45, 46]. The clinical and radiographic findings of metronidazole-induced encephalopathy are usually reversible with discontinuation of the antibiotic, although severe persistent sequelae can occur [47].

Splenial High-Signal Lesion

For about the last 10 years, the MRI finding of an ovoid or round lesion within the splenium of the corpus callosum (high signal on FLAIR/T2 and often also on DWI) has been described as a nonspecific finding associated with a variety of encephalopathic syndromes, including those due to various metabolic disorders, viral infections (termed "encephalitis/encephalopathy"), and the use of, or withdrawal from, antiepileptic agents [48, 49]. Patients with this imaging finding may have nonspecific encephalopathic symptoms including drowsiness, confusion, and agitation. Splenial high-signal lesions typically resolve on follow-up imaging in parallel with the patient's clinical resolution. Although nonspecific, this MRI finding can nonetheless be a useful finding supportive of a probable reversible metabolic (or viral) encephalopathic syndrome, and despite its usual DWI positivity, should not be confused with a cerebrovascular ischemic process affecting the corpus callosum.

Treatment

Treatment of the various encephalopathic syndromes has been discussed within the individual sections above. A general approach to management of the encephalopathic patient is, however, reviewed here.

As discussed at the outset of this chapter, initial evaluation and treatment of the encephalopathic patient should focus on keeping a strong clinical suspicion for those causes of encephalopathy that will lead to irreversible neurologic dysfunction if not recognized and reversed immediately. Therefore, the immediate approach to treatment of any encephalopathic patient is directed at correction of any circulatory deficiency and replacement of any potentially deficient metabolic substrate (e.g., oxygen, thiamine, or glucose). This should be followed by correction of any other potentially causative metabolic abnormality, treatment of any underlying causative acute systemic illness or complication of organ failure, and attempt at discontinuation or removal of any likely offending medication or toxin.

Since toxic-metabolic encephalopathies are due, by definition, to an underlying systemic process or medication (even if still unknown in the individual patient), management should focus on diagnosis and treatment of systemic dysfunction and removal of potential offending agents while attempting to minimize any CNS-active or sedating medications which might complicate or worsen the encephalopathy.

Conclusion

Neurologists are frequently asked to evaluate patients with encephalopathies. As reviewed in this chapter, in many cases a specific etiological diagnosis can be made through history, examination, laboratory studies, and in some cases, imaging, which may lead to a specific medical intervention, more rapid clinical resolution, and may help prevent irreversible neurologic dysfunction. Physicians should approach each patient with encephalopathy with an especially high level of suspicion for those causes which may lead to incomplete neurologic recovery if not specifically and expeditiously diagnosed and treated.

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Acute Respiratory Failure in Neuromuscular Disorders

16

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Abstract

Respiratory failure can be the presenting symptom of a neuromuscular disorder or occur in a patient with a known neuromuscular disorder. The signs and management of respiratory failure in these patients can be different than in patients with acute respiratory failure of other etiologies. This chapter will review the pathophysiology, clinical presentation, diagnosis, differential diagnosis, and treatment and prevention of acute respiratory failure in neuromuscular disorders.

Keywords

ALS • Lambert–Eaton's syndrome • Myasthenia gravis • Respiratory failure in neuromuscular disorders

Overview

Respiratory failure is a common cause of mortality and morbidity in patients with neuromuscular disorders. Respiratory failure can be the presenting symptom of the neuromuscular disorder. Other times there will be a known neuromuscular disorder. Timely recognition and treatment of acute respiratory failure is important in preventing complications and improving outcomes. Adequate monitoring and use of preventive measures in patients with known neuromuscular disorders is as equally important. This chapter will review the pathophysiology, clinical presentation, diagnosis, differential diagnosis, and treatment and prevention of acute respiratory failure in neuromuscular disorders.

Epidemiology

The two most common causes of acute respiratory failure secondary to neuromuscular disorders presenting to the emergency department are myasthenia gravis (MG) and Guillain–Barré syndrome (GBS) [1]. Approximately 30% of patients with GBS will require mechanical ventilation [2]. Patients with GBS who require mechanical ventilation have been shown to have a mortality rate of 20% [3]. Of 2,014

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patients admitted for myasthenia crisis between 2000 and 2005 in a nationwide study, 21.5% required endotracheal intubation, and 6.5% required noninvasive positive airway pressure [4]. Age, diagnosis of MG crisis, and respiratory failure requiring endotracheal intubation were major predictors of death. Overall hospital mortality rate for all myasthenia gravis admissions was 2.2% and 4.4% among patients admitted for myasthenia crisis.

Pathophysiology

The mechanisms of breathing consist of two primary components: the respiratory motor unit and the central network of neurons coordinating breathing. Neuromuscular disorders affect the respirator motor unit, while strokes, tumors, and degenerative brain diseases affect the central network. The central network includes the pontine respiratory group, the dorsal respiratory group (DRG), and the ventral respiratory group [5].

Carotid chemoreceptors detect a change in O_2. A decrease in O_2 stimulates the DRG, which is located in the nucleus of the solitary tract. The DRG also receives excitation from central CO_2 chemoreceptors in the medulla [5, 6]. In addition, the nucleus of the solitary tract receives input from baroreceptors and cardio receptors. The VRG consists of a group of neurons that contain expiratory and inspiratory neurons. The Bötzinger complex, the most rostral portion of the VRG, inhibits inspiratory neurons in the VRG and projects to expiratory neurons in the spinal cord. Just caudal to the Bötzinger complex is the pre-Bötzinger complex, which plays an important role in respiratory rhythm generation [5, 7, 8]. Caudal to the pre-Bötzinger complex are inspiratory bulbospinal neurons of the VRG. The most caudal portion of the VRG contains expiratory bulbospinal neurons [5]. The VRG extends from ventrolateral medulla to C1 cervical cord. Respiratory phase timing, integration of reflexes from pulmonary mechanoreceptors, and relay station from medullary respiratory neurons to hypothalamus, amygdala, and other suprapontine structures occur in the pontine respiratory group [5]. Descending neurons from the respiratory centers are located in the anterolateral white matter and connect to respiratory motor neurons in the spinal cord [5]. Autonomic respiratory neurons travel closely to the spinothalamic tract, while voluntary respiratory neurons travel near the corticospinal tracts [5].

The respiratory motor unit includes the anterior horn cell, axon, neuromuscular junction, and muscle fibers the motor neuron innervates. Inspiratory nerves and muscles include the phrenic nerve to the diaphragm, intercostal nerves to the external intercostal muscles, cervical spinal nerves to the scalene muscles, and spinal accessory nerve (cranial nerve XI) to the sternocleidomastoid. Expiratory nerves and muscles include intercostal nerves to the internal intercostal muscles, and lower thoracic and lumbar spinal nerves to the rectus abdominis, obliques, and transversus abdominis muscles. In a normal individual, expiratory muscles are generally not needed and are more important for generating adequate cough.

Respiratory muscles require enough strength to overcome the elastic load, which encompasses upper airway resistance, abdominal pressure, and chest wall and lung compliance. Obesity and weakness of oropharyngeal muscles increase upper airway resistance. Abdominal pressure will rise with distension (i.e., constipation). Lung compliance decreases secondary to microatelectasis [9]. Microatelectasis contributes to ventilation–perfusion mismatch and further restriction of pulmonary compliance [10–12]. Chest wall compliance is increased in children with neuromuscular disorders 3 months to 4 years of age, which can lead to chest wall deformities and possibly reduced lung growth [9, 13]. As adults, chest wall compliance decreases secondary to deformities, scoliosis, and increased stiffness of rib cage [9, 14, 15]. A change to any one of these will increase demand on the respiratory muscles.

Respiratory failure in neuromuscular patients can occur from three main mechanisms (1) aspiration secondary to oropharyngeal weakness, (2) fatigue of respiratory muscles, and (3) weak cough. Weakness in oropharyngeal muscles will impair the ability to swallow and protect the airway, placing the patient at increased risk for aspiration.

This can lead to recurrent pneumonias and parenchymal disease.

Fatigue of respiratory muscles occurs when strength has fallen below 25–30% of normal [11]. Of all the inspiratory muscles, the diaphragm performs the majority of the work and accounts for about 70% of the inspiratory effort at rest [11]. Therefore diaphragmatic fatigue plays a major role in respiratory failure in neuromuscular patients. Diaphragmatic fatigue will occur in less than 60 min when the pressure it must produce (Pdi) is greater than 40% of the maximum pressure it can generate (Pdi_{max}), or when the ratio of time the diaphragm must contract (Ti) to total respiratory cycle (T_{tot}) is 0.5 [9, 16]. Decreased lung and wall compliance will increase Pdi while muscle weakness will decrease the Pdi_{max}. However, the Ti/T_{tot} also plays an important role in diaphragmatic fatigue. Endurance time (T_{lim}) is inversely related to Ti/T_{tot} [17]. An increase in respiratory rate (RR) secondary to fever, illness or to compensate for hypercapnia and an increase in upper airway resistance secondary to oropharyngeal weakness will increase the Ti/T_{tot} ratio and lead to fatigue sooner. Tension–time index of the diaphragm (TTdi), which is the time integral of diaphragmatic tension per breath, may be a better indicator for predicting respiratory failure because it takes into consideration Ti/T_{tot} and Pdi/Pdi_{max}. TTdi is calculated by multiplying Ti/T_{tot} by Pdi/Pdi_{max}. A TTdi above 0.15 was found to have T_{lim} less than 45 min and therefore $TTdi_{crit}$ is 0.15 [17]. Tension–time index of the rib cage muscles (TTrc) has also been calculated with a higher critical value of 0.30 [18]. However, the importance of TTrc in the clinical setting is unclear.

Normal response to parenchymal disease and/or hypercapnia is to increase minute ventilation. Patients with neuromuscular disease have a normal central drive response to hypercapnia and hypoxemia as controls; however, the mechanism of increasing minute ventilation is different [9, 19, 20]. Normal controls increase tidal volume more than RR, while neuromuscular patients increased RR [9, 20]. This may in part relate to neuromuscular patients having a decrease Pdi_{max}.

An adequate cough is also important in maintaining respiratory function. Without an adequate cough, secretions cannot be cleared leading to atelectasis, mucus plugs, and pneumonias. An adequate cough requires good inspiratory effort (60–90% of total lung capacity), glottic closure, and good expiratory effort [9]. An abnormality in any one of these will lead to an impaired cough.

Clinical Presentation

Clinical signs of respiratory failure can be different depending on the rate of respiratory failure. Patients with chronic neuromuscular disease will usually develop sleep complaints first and are less likely to complain of dyspnea. Patients with a more rapid progression will notice dyspnea, orthopnea, and staccato speech (needing to take breaths between words) [11]. Preceding infection or illness can often be a precipitating factor to respiratory failure.

Sleep difficulties can be the first presenting sign of respiratory muscle involvement in chronic neuromuscular diseases. Sleep difficulties can be a result of obstructive sleep apnea (OSA) or nocturnal sleep-related hypoventilation [21, 22]. Patients with oropharyngeal weakness are at risk of developing OSA. Symptoms can include snoring, fragmented sleep, excessive daytime sleepiness, frequent urination, nonrestorative sleep, hypertension, congestive heart failure, and pulmonary hypertension. Although snoring can often be heard in OSA, OSA can occur without the presence of snoring. A more common sleep-related breathing disorder among neuromuscular disorders is nocturnal hypoventilation. As the diaphragm becomes weaker, patients rely more on accessory respiratory muscles. Normally, during Rapid Eye Movement (REM) sleep, the body is paralyzed except for the diaphragm and eye movements. Therefore, patients with diaphragm weakness, who rely on accessory muscles to maintain adequate ventilation, will usually develop hypoventilation during REM sleep initially. As the weakness progresses, hypoventilation can be seen in all stages of sleep. Symptoms of nocturnal hypoventilation are similar to OSA; however, nocturnal hypoventilation is more likely to result in nocturnal confusion, morning confusion, and morning headaches secondary to hypercapnia.

Insidious onset of orthopnea can also make sleeping difficult. As sleep complaints are often the first sign of chronic respiratory insufficiency, a detailed sleep history is important when evaluating a patient with a neuromuscular disease.

Independent of time and course of respiratory insufficiency, signs of impending failure include dyspnea at rest, tachypnea, orthopnea, staccato speech, use of accessory muscles, forehead sweating, profound neck flexion weakness, paradoxical breathing, and vague sense of anxiety or discomfort [10]. One exception to orthopnea would be a patient with primarily intercostal and accessory muscle weakness, such as in patients with spinal muscular atrophy (SMA). These patients rely heavily on the diaphragm and have more difficulty with exhalation rather than inhalation. In the supine position, the diaphragm has an increased mechanical advantage to assist with exhalation. Therefore patients with SMA may benefit from placement in the Trendelenburg position [23].

Other signs of impending respiratory failure can be related to oropharyngeal weakness or weak cough. These patients are at risk for aspiration and/or pneumonia. Coughing after drinking or eating can be a sign of aspiration. Trouble with increased oral secretions is a sign of difficulty swallowing, while a weak cough increases the difficulty in getting secretions up. Therefore, it is important to be aware of the wide range of symptoms of respiratory insufficiency in neuromuscular patients, from trouble sleeping, coughing after meals, to severe dyspnea, orthopnea, and tachypnea.

Diagnosis

Diagnosis of respiratory failure in neuromuscular diseases can be broken down into diagnosing a neuromuscular cause of respiratory failure compared to other causes of respiratory failure and diagnosing the type of neuromuscular disease. In the acute emergent situation, diagnosis of type of respiratory failure is imperative. However, early diagnosis of type of neuromuscular disease is also essential when initiating treatment and for prognosis.

The majority of patients with neuromuscular diseases that cause respiratory failure will have findings of other muscle involvement on physical examination, specifically weakness of neck flexion, proximal muscles, and bulbar muscles. However, there are a few exceptions, such as Pompe's disease, that can present with isolated respiratory muscle weakness. A detailed history and examination can provide evidence of a neuromuscular cause of respiratory failure. For example, paradoxical breathing in the supine position suggests diaphragm weakness. In addition to history and physical examination, the diagnosis of neuromuscular weakness as the cause of respiratory failure may require ancillary tests.

Objective tests to aid in the diagnosis of respiratory failure secondary to neuromuscular weakness include arterial blood gas (ABG), Pulmonary Function Tests (PFTs), chest imaging, electrocardiogram (ECG), and blood work. In a hypoxic patient, an ABG should demonstrate elevations of $PaCO_2$. One should question respiratory muscle weakness as a cause of hypoxemia without hypercapnia. Hypoxemia can be seen without hypercapnia in a neuromuscular patient when the hypoxemia is secondary to pneumonia or aspiration. With acute respiratory failure due to respiratory muscle weakness, the ABG should demonstrate a decrease in pH, elevation in $PaCO_2$, minimal rise in bicarbonate level, and depending on the severity, a decrease in PaO_2. With chronic respiratory failure, there is a greater bicarbonate rise and a less significant decrease in pH. However, in patients with only sleep-related hypoventilation, the ABG may demonstrate a normal $PaCO_2$ and PaO_2 with mildly elevated pH and bicarbonate level. Although an ABG is extremely helpful, specifically in a hypoxic patient, the ABG may be normal in the early stages of the disease. Therefore, an ABG alone is not enough to diagnose or monitor a patient with respiratory muscle weakness.

PFTs are an extremely important tool in diagnosing and monitoring patients with neuromuscular disease. Although full PFTs usually demonstrate a restrictive pattern, their value in the acute setting is limited. However, forced vital

capacity (FVC), maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP), and peak cough flows (PCFs) can be performed at the bedside. Healthy, nonobese controls have less than a 10% drop in FVC in the supine position compared to the sitting position [24]. A drop of more than 15–20% in the supine position is a strong indicator of diaphragm weakness [11, 12]. An absolute decrease in FVC is not specific to neuromuscular weakness; however, a FVC of less than 20 mL/kg is a strong predictor for mechanical ventilation [12]. The MIP reflects the strength of all inspiratory muscles. A normal MIP (< −80 cm H_2O in males and < −70 cm H_2O in females) excludes significant respiratory muscle weakness [11]. While the MEP reflects the strength of expiratory muscles, the MEP differs from PCFs in that the MEP measures the peak pressure and PCFs measure the peak flow. Adults require PCFs of >160 L/min to clear secretions [25–27]. Major limitations of PFTs are that they require a good oral seal, which patients with bulbar weakness may not be able to obtain, and are effort dependent.

A single breath count can also be a useful tool in assessing vital capacity (VC). The patient counts out loud with one breath. Normally one should reach 50. A count less than 15 suggests severe decrease in VC; however, it is not specific for a neuromuscular cause of decreased VC [12]. In general if the patient can count to 10 with a single breath, the VC is about 1 L and counting to 25 suggests a VC of approximately 2 L.

Chest imaging cannot only assist with the diagnosis of respiratory muscle weakness, but can also aid in ruling out other causes of respiratory failure. An upright chest X-ray can demonstrate an elevated diaphragm with diaphragmatic weakness, which is most useful in unilateral diaphragmatic paralysis. Chest X-ray can also aid in the evaluation of pneumonia, congestive heart failure, and mass lesions. The Sniff test evaluates diaphragmatic movement under fluoroscopy, which can be extremely valuable. CT of the chest aids in evaluation of pneumonia, parenchymal lung disease, mass lesions, and pulmonary emboli (PE). Nonambulatory patients are at an increased risk for developing a PE and therefore a PE needs to be considered in any unexpected acute respiratory failure.

It is also important to rule out other causes of respiratory failure. ECG and cardiac enzymes should be considered to evaluate for a cardiac cause of symptoms, especially as many neuromuscular disorders also have significant cardiac abnormalities, e.g., Pompe's disease, Duchenne's muscular dystrophy, myotonic dystrophy, and mitochondria myopathies. Severe electrolyte abnormalities can cause neuromuscular weakness; therefore, chemistries, including calcium, phosphorus, and magnesium, are important and crucial to the evaluation. Creatine kinase (CK) can be elevated in myopathies as well as mildly elevated in severe neurogenic disorders, such as ALS. In the presence of altered mental status, a complete metabolic workup, including urine toxicology, is indicated.

Electromyography (EMG) with nerve conduction studies (NCS) can be essential to the diagnosis of a neuromuscular disease. However, the utility of EMG/NCV in the acute setting is limited for a number of reasons. First, quality studies require an electrically quite environment. Intensive care units and emergency rooms have electrical beds, IV pumps, monitors, ventilators, and compression stockings. All of these devices contribute to the 60 Hz artifact, consequently affecting the ability to record quality wave forms. Secondly, depending on the time since onset of symptoms, it may take 2 weeks or more to find significant abnormalities on EMG.

Polysomnography (PSG) is useful in diagnosing sleep-related breathing disorders in patients with neuromuscular diseases without significant daytime breathing difficulties, either clinically or by PFTs. The first abnormality in sleep-related hypoventilation is a rise in CO_2, defined by more than 10 cm H_2O, most often during REM sleep. CO_2 can be monitored during PSG by either transcutaneous CO_2 or end tidal CO_2. However, a "routine" PSG does not usually record CO_2. Therefore it is important to specify the type of PSG requested on a neuromuscular patient. Due to comorbid diseases, or when CO_2 increases significantly, O_2 saturations will decrease. The decrease in O_2 is a continuous drop rather than

repeated dips as seen with OSA. The hypoxemia will usually first occur during REM sleep. Routine overnight oximetry can detect hypoxemia, but cannot detect hypercapnia and OSA without desaturations. PSG is important in the titration of positive airway pressure, either in the form of continuous positive airway pressure (CPAP) or bilevel positive airway pressure for the treatment of sleep-related hypoventilation.

Differential Diagnosis

Once there is a diagnosis of respiratory failure secondary to neuromuscular weakness, the next step is to determine the cause of neuromuscular weakness. Often the patient will already have a history of a neuromuscular disease. However, in some cases the first presenting symptom will be respiratory failure. Differentiating the cause of weakness involves a detailed history and detailed neurological examination, followed by the appropriate ancillary test to confirm or narrow the number of disorders in the differential diagnosis.

The first step in diagnosing the etiology of the symptoms involves a detailed history. Is there a history of a neurological disorder? Many patients with ALS, muscular dystrophy, myotonic dystrophy, and myasthenia gravis already have a diagnosis. However, this is not always the case, although there may be clues of a progressive neuromuscular disorder, e.g., falls, trouble swallowing, talking, weakness, weight loss, and dyspnea. In patients with a known risk of developing respiratory failure, investigate the possibilities of what may have triggered the respiratory failure, such as infection, aspiration, medication, or expected progression of the underlying disease. Does the patient have weakness other than in the respiratory muscles? Where did the weakness start? Weakness beginning in the legs and ascending up to the arms is typical of GBS, while prominent bulbar or cranial nerve weakness is suggestive of MG or botulism. Inquire about other neurological symptoms, such as numbness, double vision, cognitive disturbance, cramps, pain, fasciculations, or seizures. Numbness and sensory loss suggest a neurogenic disorder rather than a myopathy or disorder of the neuromuscular junction. Recent medications, drug, or toxin exposures are important to ascertain, as is a history of an insect or snake bite. Systemic symptoms or disorders including lung cancer may suggest a vasculitic neuropathy or Lambert–Eaton's myasthenic syndrome (LEMS). Abdominal pain may suggest porphyria. At times in the emergency setting the history may be incomplete especially if the patient is unresponsive. However, family and/or friends can be extremely helpful in providing significant details in the history of a neurological patient.

The second step in determining the etiology involves localizing the neurological problem. Neuromuscular weakness can localize to the anterior horn cell, nerve root, plexus, nerve, neuromuscular junction, or muscle. The neurological examination is fundamental to localization. Increased reflexes and spasticity suggest an upper motor neuron disorder. Decreased reflexes, fasciculations, decreased tone, and atrophy are signs of a lower motor neuron disorder. The presence of both upper and lower motor neuron signs suggests ALS. The distribution of weakness can assist in localization. Symmetrical proximal weakness suggests a myopathy, while distal weakness is more common in polyneuropathies. Variable or fluctuating weakness is indicative of a disorder of the neuromuscular junction, while sensory abnormalities favor a peripheral neuropathy as opposed to a disorder of muscle or neuromuscular junction. Despite a detailed neurological examination, there are times when it is still difficult to localize the process with complete certainty. EMG and NCS are an extremely useful adjunct to the neurological examination in localizing lower motor neuron abnormalities.

An EMG can provide information on pathophysiology, severity, evolution, and chronicity. It may confirm or exclude a diagnosis or identify an unrecognized disease. The muscles involved in a neurogenic process can assist in localizing the abnormality. The NCS evaluates not only motor nerves, but large-fiber sensory nerves as well. Conduction velocities, presence of conduction block, or dispersion on NCS provide information on the myelination of the nerve.

Further ancillary testing will depend on the differential diagnosis. For disorders localizing to the muscle, see Table 16.1 for differential diagnosis. The majority of myopathies will have small complex motor unit potentials (MUPs) on EMG. However, the definitive diagnosis will usually require a muscle biopsy. For disorders localizing to the neuromuscular junction, see Table 16.2.

Table 16.1 Disorders causing neuromuscular respiratory weakness localizing to the muscle

Disorder	Key clinical findings	Key test
Acid maltase deficiency (Pompe's disease) [28]	– Significant respiratory muscle involvement – Cardiac involvement prominent in children – Adults slow course with early diaphragm involvement – Axial/paraspinal weakness – Scapular winging	– EMG: myopathic findings with myotonic discharges; findings may only be in paraspinal muscles – Alpha-glucosidase deficiency in leukocytes, fibroblasts, or muscle – Genetic testing
Congenital muscular dystrophy [29]	– Hypotonia and weakness at birth – Almost always fatal during childhood or adolescents	– Normal to Increase CK – Muscle biopsy
Congenital myopathy [5, 11, 30]	– Hypotonia and weakness as infant – Respiratory failure most likely in nemaline myopathy, multiminicore disease, and myotubular myopathy and less likely central core disease	– Muscle biopsy
Idiopathic nemaline myopathy [31]	– Proximal to generalized weakness – Complication of HIV [32], monoclonal gammopathy [33, 34], or hypothyroidism [35]	– HIV – UPEP-Urine Protein electro phoresis – TSH – Muscle biopsy
Dystrophinopathy	– Progressive weakness starting in childhood – Cardiomyopathy – Calf pseudohypertrophy – X-linked	– Marked Increase CK (50–100 × normal) – Dystrophin gene testing
Myofibrillar myopathy [5]	– Distal myopathy – Usually adult onset – Cardiac abnormalities	– Muscle biopsy
Bethlem's myopathy [36]	– Muscle cramps and weakness – Contractures common – Autosomal dominant	– Muscle biopsy
Myotonic dystrophy	– Distal and bulbar weakness more prominent – Male pattern baldness – Cardiac abnormalities – Myotonia on exam – Autosomal dominant	– Myotonic discharges on EMG – Mutation in DMPK gene (type 1) – Mutation in CNBP (type 2)
Mitochondrial myopathy [37]	– Ophthalmoparesis indolent – Generalized weakness – Hearing loss – Cardiomyopathy	– Increase Lactic acid level – Muscle biopsy may show ragged red fibers
Limb-girdle muscular dystrophy (especially 2C, 2F, 2L) [5, 11]	– Pelvic and should girdle weakness – Usually present in adults	– Muscle biopsy – Normal to Increase CK
Inflammatory myopathy	– Proximal muscle weakness – Muscle pain – Skin rash with dermatomyositis	– Increase CK – Muscle biopsy – Screen for possible malignancy

(continued)

Table 16.1 (continued)

Disorder	Key clinical findings	Key test
Inclusion body myositis [38–40]	– Significant flinger flexor weakness – Onset typically over age 50 – Years of slow progression – Disproportionate quad weakness/ atrophy	– Muscle biopsy – Mild Increase CK
Toxic [41, 42]	– Muscle pain – Generalized weakness – Alcohol, cholesterol-lowering agents, colchicine, chloroquine, cyclosporine, L-tryptophan, zidovudine	– Marked Increase CK – Phosphate level – Liver function test
Metabolic myopathy with myoglobinuria [43]	– Muscle pain – Swelling – Rhabdomyolysis – Carnitine palmitoyl transferase deficiency – Glycolytic enzyme defects	– Marked Increase CK following exercise – Myoglobinuria – Monitor renal function – Ischemic exercise test
Periodic paralysis	– Hereditary – Associated with thyrotoxicosis [44] – Episodic weakness – *Andersen–Tawil's syndrome* (*prolonged QT*)	– Check K level – ECG – Normal or Increase CK – TSH
Trichinosis myositis [45]	– Cardiomyopathy – Severe weakness – Periorbital and facial edema	– Increase CK – Eosinophilia – Muscle biopsy demonstrated larvae of *Trichinella spiralis*
Critical illness myopathy [46]	– History of multiorgan failure – Steroid or neuromuscular blocking agents – Failure to wean off ventilator	– Usually normal Increase CK – EMG may be normal – Muscle biopsy

Table 16.2 Disorders causing neuromuscular respiratory weakness localizing to the neuromuscular junction

Disorder	Key clinical findings	Key test
Myasthenia gravis	– Ocular muscle weakness – Bulbar weakness – Fatigable weakness – Normal pupil function	– Acetylcholine receptor antibodies – Anti-muscle-specific kinase (MuSK) antibody [47] – Decrement on 2 Hz repetitive stimulation – Increase jitter on single fiber
Lambert–Eaton's myasthenic syndrome (LEMS)	– Limb weakness – Autonomic symptoms – Strength gets better with brief exercise	– Anti-VGCC – Decrement on 1–5 Hz repetitive stimulation – Facilitation on 30–50 Hz repetitive stimulation – Screen for possible malignancy
Organophosphate poisoning [48]	– Weakness proximal > distal – Diarrhea and cramping – Increase salvation	– Spontaneous repetitive firing of compound muscle action potential after single stimulation
Botulism	– Ophthalmoplegia – Pupil affected – Nausea, vomiting, abdominal pain – Generalized weakness – Autonomic symptoms	– EMG similar to LEMS – Detection of botulinum toxin in blood or stool
Hypermagnesemia [49]	– Renal failure – History of magnesium intact	– Mg level – Bun, Cr, urinalysis

Decrement on 1–5 Hz repetitive stimulation suggests a disorder of the neuromuscular junction. Postsynaptic disorders usually demonstrate a greater decrement than presynaptic disorders. Facilitation, defined as an increase in more than two times the baseline amplitude of the compound muscle action potential (CMAP), can be demonstrated with 10 s of exercise or 30–50 Hz repetitive stimulation in presynaptic disorders. Increased jitter on single-fiber EMG can be seen in all types of neuromuscular junction disorders. For disorders localizing to the peripheral nerve, see Table 16.3. Sensory abnormalities on NCS are key findings to localize the abnormality to the peripheral nerve or plexus. Slowed conduction velocities and conduction block suggest a demyelinating neuropathy, while decreased CMAP amplitudes, with normal-to-mild slowing of conduction velocities, suggest axonal neuropathy. Disorders localizing to the motor neuron (Table 16.4) will spare sensory NCS. There are some disorders, specifically neurotoxins, which can affect the motor neuron, neuromuscular junction, and/or muscle (Table 16.5). These disorders can demonstrate a mixture of findings on NCS and EMG.

Table 16.3 Disorders causing neuromuscular respiratory weakness localizing to the peripheral nerve

Disorder	Key clinical findings	Key test
Guillain–Barré syndrome	– Progressive weakness, usually ascending – Peak weakness by 2–3 weeks – Dysesthesias in feet and hands – Areflexia – Autonomic symptoms	– CSF elevated protein – Anti-GM1 seen with *Campylobacter jejuni* infection – Anti-GQ1b seen in Miller–Fisher's variant – NCS demonstrate slowed conduction velocities, prolonged F waves, and reduced CMAP
Porphyria [50]	– Abdominal pain – Weakness(arms > legs) – Autonomic symptoms – Triggered by infection, alcohol, stress, smoking, and P450-inducing drugs	– Urine porphyrin, porphobilinogen, and δ-aminolevulinic acid levels – EMG demonstrates primarily motor axonal neuropathy
Neuralgic amyotrophy [51]	– Severe shoulder and arm pain – Weakness and numbness in arm follows pain – Can have isolated phrenic nerve involvement	– EMG consistent with a brachial plexus lesion
Vasculitic neuropathy [52]	– Multiple mononeuropathies or asymmetric polyneuropathy – Painful – Sensory loss – May have symptoms of systemic vasculitis	– ESR – CBC – ANA – RF – ANCA – Urinalysis – Complement levels – Hepatitis screen – HIV – Cryoglobulins – Nerve biopsy
Critical illness polyneuropathy [46]	– History of multiorgan failure or sepsis – Steroid or neuromuscular blocking agents – Failure to wean off ventilator	– EMG: axonal sensorimotor polyneuropathy

(continued)

Table 16.3 (continued)

Disorder	Key clinical findings	Key test
POEMS syndrome [53]	– Polyneuropathy – Organomegaly – Endocrinopathy – M-protein spike – Skin changes	– SPEP – UPEP – EMG: sensorimotor polyneuropathy
Multifocal motor neuropathy with conduction block [54]	– Asymmetrical limb weakness – Upper extremities > lower extremities	– Anti-GM1 – NCS demonstrate conduction block
Arsenic poisoning [55]	– Encephalopathy – Symmetrical neuropathy – Painful	– EMG shows primarily axonal, sensorimotor neuropathy – Urine arsenic level
Diphtheria [56]	– History of sore throat – CN involvement – Pupil abnormalities	– Throat culture for *C. diphtheriae* – CSF elevated protein and pleocytosis – NCS similar to GBS

Table 16.4 Disorders causing neuromuscular respiratory weakness localizing to the motor neuron

Disorder	Key clinical findings	Key test
Amyotrophic lateral sclerosis	– Upper and lower motor findings – Progressive weakness without significant pain or sensory symptoms – Fasciculations	– EMG: diffuse fibrillation potentials, fasciculation potentials, and neurogenic MUPs
Poliomyelitis and postpolio syndrome [57]	– Asymmetrical weakness – Fever and meningismus – History of poliomyelitis usually affecting bulbar or respiratory muscles	– CSF: elevated protein and pleocytosis – EMG: neurogenic MUPs
Spinal muscular atrophy (types 1> 2> 3) [23]	– Proximal > distal weakness – Decrease deep-tendon reflexes – Intercostal muscle weakness >> diaphragm weakness	– Gene testing for SMN1 – EMG: neurogenic MUPs, normal sensory NCS

Table 16.5 Disorders causing neuromuscular respiratory weakness affecting multiple locations

Disorder	Key clinical findings	Key test
Scorpion venom [58, 59]	– History of sting – Muscle jerks and restlessness – Tachycardia and tachypnea – Hyperpyrexia – Excessive salivation	– Elevated WBC
Tick Paralysis [60]	– Ascending flaccid paralysis (hours to few days) – Ataxia	– Search and remove tick
Seafood toxins [43, 61] (ciguatera and saxitoxin)	– History of recent seafood ingestion – Nausea, vomiting, and diarrhea – Paresthesia face and mouth – Generalized weakness	– Diagnosis made clinically – Commercially available toxin assays are currently not available

Treatment

The initial priority in the treatment of neuromuscular respiratory failure includes ventilation, protecting the airway, and clearing secretions. The second priority involves treating the underlining disease, if treatment is available, or treating precipitating factors (i.e., pneumonia). The third priority in treatment involves implementation of preventative strategies in patients with known neuromuscular disorders.

Ventilation is the primary treatment for respiratory failure secondary to neuromuscular weakness. The optimal method of ventilation will depend on the condition of the patient and the type of neuromuscular disease. In general (and contrary to common practice for patients with respiratory insufficiency), neuromuscular patients should not be put on oxygen without some mode of secure or enhanced ventilation. Patients with chronic hypoventilation may have a chronic elevation of pCO_2 leading to a "hypoxic drive" of respiration. Treatment with supplemental oxygen raises the pO_2 resulting in loss of the "hypoxic drive." Subsequently the patient further hypoventilates leading to increasing levels of CO_2. Such patients often appear "more comfortable" in part because of the sedating effects of hypercapnia. As such sedation becomes increasingly profound over the next few hours, the patient follows a vicious cycle of increased sedation leading to reduced ventilation, which in turn raises the pCO_2 even further, producing increasing sedation and ultimately a respiratory arrest. In patients with hypoxemia secondary to aspiration or pneumonia without any respiratory muscle weakness or elevated CO_2, oxygen alone may be appropriate. However CO_2 levels need to be monitored very closely in these patients to ensure adequate ventilation.

Invasive ventilation is generally recommended for reversible neuromuscular weakness and acute respiratory failure. An FVC of less than 15 mL/kg, oropharyngeal weakness with aspiration, or PO_2 less than 70 mm Hg are the accepted absolute criteria for intubation in patients with GBS [62]. Impaired consciousness, respiratory or cardiac arrest, shock, arrhythmias, and blood gas abnormalities are also accepted absolute criteria for intubation in all patients [12]. In patients who do not meet the absolute criteria for intubation, the decision to intubate is more difficult. Patients to be considered for intubation include those having dyspnea at rest, tachypnea, orthopnea, staccato speech, tachycardia, accessory muscle use, weak cough, cough after swallowing, markedly weakened neck muscles, bulbar dysfunction, or dysautonomia [10, 12, 63]. These patients need to be monitored very closely, ideally in the ICU, and elective intubation should be performed prior to complications from respiratory failure and abnormalities on ABG. Monitoring should include vital signs, bedside PFTs, clinical symptoms, and bulbar, neck, and extremity weakness. Patients with rapidly progressive GBS are also at an increased risk for acute respiratory failure [63]. Bedside PFTs can assist in predicting those patients at risk for acute respiratory failure. A VC less than 20 mL/kg, MIP worse than −30 cm H_2O, MEP less than 40 cm H_2O, or 30% drop in VC, MIP, or MEP indicate a risk for respiratory failure in GBS [64]. One simple bedside estimate of FVC is the counting test. The patient is asked to take a maximal breath in and count out loud as far as possible on one breath. The ability to count to 10 suggests a FVC of 1 L and counting to 25 on one breath suggests a FVC of 2 L. The clinician must be cautious when interpreting bedside spirometry (FVC, MIP, and MEP) in neuromuscular patients. Often when patients have severe weakness of facial muscles, they will be unable to maintain a seal around the mouthpiece resulting in falsely low values. Also those patients with corticobulbar tract upper motor neuron disease (as is seen with ALS) may be unable to volitionally integrate the necessary components for a reliable measurement (similar to an apraxia) resulting in unreliably low values. It behooves the clinician to conduct a bedside assessment to assure that the spirometry measurements are consistent with the patient's clinical status. In patients with MG, repetitive measurements of VC correlate less well with the need for mechanical ventilation [65]. When intubating a neuromuscular patient, depolarizing neuromuscular blocking agents

should be avoided secondary to potentially life-threatening hyperkalemia [66, 67]. It is recommended to use topical anesthesia, short-acting benzodiazepines, and, if needed, atropine when intubating a neuromuscular patient [12].

Noninvasive positive pressure ventilation (NPPV) may be an alternative to mechanical ventilation for those patients without oropharyngeal weakness or expected prolonged need for mechanical ventilation, although the use of NPPV in the acute respiratory setting has not been well studied. Bilevel positive airway pressure allows for establishing the expiratory pressure (EPAP) and inspiratory pressure (IPAP), with IPAP being high enough over EPAP to effectively ventilate the patient. The differential of IPAP to EPAP needed to ventilate a patient will depend on the elastic load of the lungs and chest wall. If the patient's weakness is severe enough where the patient cannot trigger the pressure-support breaths or the patient has central apnea, then a spontaneous/timed (S/T) mode is indicated and will provide a minimum respiratory rate. When bilevel positive airway pressure cannot adequately ventilate a patient or the patient cannot tolerate bilevel positive airway pressure, there must be consideration for mechanical ventilation either with volume-cycle mask ventilation (close circuit versus the open circuit with bilevel) or invasive ventilation. However, in an emergent situation, invasive ventilation is more appropriate, especially if there is a risk for aspiration secondary to bulbar weakness or decreased level of consciousness.

NPPV may limit complications from invasive ventilation. Mortality, ICU stay, and complication rates were lower in a small retrospective series of chronic progressive neuromuscular patients with acute respiratory failure treated with NPPV compared to historical controls treated with invasive ventilation [68]. Those patients with difficulty clearing secretions using NPPV received a cricothyroid "minitracheostomy" (CM). The CM allows tracheal access to suction secretions. Benefits of NPPV include enabling the patient to eat and speak. Preservation of communication is an obvious priority in patients with progressive neuromuscular diseases. Patients on NPPV have the ability to participate in medical decision making, while a patient with endotracheal intubation will require sedation limiting their ability to make important medical choices. Occasional patients with progressive neuromuscular disorders, who undergo tracheostomy without their consent, would have chosen not to have the tracheostomy if given the opportunity to make their own medical decisions [69]. NPPV also spares some patients with MG from intubation [70]. However, hypercapnia greater than 50 mm Hg predicts failure of NPPV.

Cough augmentation devices, either manual or mechanical, can help with clearing the airway when patients have a weak cough. Manual cough augmentation encompasses manual hyperinflation of lungs. If expiratory muscles are weak, an abdominal thrust maneuver may increase PCFs [71]. Mechanical cough augmentation has preset insufflation and exsufflation pressures. Consider cough augmentation in patients with early respiratory infections to prevent further respiratory failure. Cough augmentation can be used as often as necessary and should be considered when there is a rapid drop in O_2 with the intent to enhance clearing of secretions.

Treatment of underlying neurological disease is the next step in treating the patient with respiratory failure. Treatment may include replacing electrolyte abnormalities, discontinuing triggering or exacerbating drugs, treating underlying infections, and supportive care. Intravenous immunoglobulin (IVIG) or plasmapheresis may be indicated, specifically for GBS and MG, while corticosteroids can be considered for inflammatory myositis or vasculitis. Avoid dehydration, fasting, and fever, each of which can increase metabolic demand and increase RR. In patients where the acute respiratory failure is secondary to progression of a noncurable disease without any exacerbating factors, decisions on long-term ventilation need to be addressed. If the patient does not wish to have long-term ventilation, comfort care is indicated. Ideally, these discussions should occur prior to acute respiratory failure.

Prevention of acute respiratory failure is important in patients with known neuromuscular weakness. Close surveillance with PFTs, use of NPPV when appropriate, and airway clearance with mechanical cough assist devices are important in preventing acute respiratory failure. High-frequency chest wall compression is typically not helpful given that most neuromuscular patients do not have difficulty with mucociliary clearance.

Routine PFTs can help anticipate patients who are at risk for respiratory failure. Recent recommendations for the management of respiratory care in the patient with Duchenne's muscular dystrophy include monitoring FVC, MIP, and PCF [66, 72]. Nocturnal NPPV should be considered in patients with decreased FVC, MIP, or MEP. Current Center for Medicare and Medicaid Services (CMS) reimbursement requirements for NPPV are that the patient must have a progressive neuromuscular disorder and one of the following: FVC <50% predicted, MIP <60 cm H_2O, $PaCO_2 \geq 45$ mm Hg, or nocturnal oximetry demonstrating O_2 saturation ≤88% for five minutes not contributed to by apneic events. In some patients, PFTs may be relatively unremarkable, but they may still suffer from significant sleep-related breathing disorders. In these patients, a polysomnogram should be considered.

Nocturnal NPPV has been demonstrated to improve quality of life, decrease hypercarbia, and increase survival rates in patients with neuromuscular disease [72–76]. Nocturnal NPPV is thought to improve respiratory function by resting muscles at night, improving microatelectasis, and possibly altering the CO_2 set point [77–79]. In young children with SMA, NPPV improves lung development and helps prevent chest wall deformities [13, 23, 80]. A new generation of bilevel machines allows the tidal volume to be set and the IPAP pressure titrated to meet the target volume. This method may theoretically be beneficial for neuromuscular disorders with a faster progression. It ensures an adequate tidal volume without having to retitrate the IPAP pressure needed to adequately ventilate a patient.

PCFs can help identify those patients who are risk for pneumonia. Adults require PCFs of >160 L/min to clear secretions [25–27]. Patients with PCFs less than 270 L/min are at risk of dropping below 160 L/min when ill, and therefore patients with PCFs less than 270 L/min are felt to be at an increased risk for recurrent pneumonias [9, 26, 81]. Patients with PCFs below 270 L/min should be monitored closely and be considered for training with cough augmentation devices. A more aggressive protocol using frequent monitoring of PFTs, home oximetry monitoring, air stacking, assisted coughing, and intermittent NPPV has been shown to decrease hospitalization in patients with neuromuscular diseases, specifically due to upper respiratory tract infections [26, 81].

Preventive measures need to be taken for elective procedures requiring sedation or anesthesia in neuromuscular patients. Depolarizing muscle relaxants and neuromuscular blockers are absolutely contraindicated because of rhabdomyolysis and fatal hyperkalemia [66, 67]. Malignant hyperthermia-like reactions can occur with inhalational anesthetics, especially in central core myopathy. Currently, it is recommended that total intravenous anesthetic techniques be used for patients with Duchenne's muscular dystrophy [66]. Patients with decreased FVC <50% are at a higher risk for respiratory failure with anesthesia and may need prolonged ventilation with either NPPV or invasive ventilation. These patients should be monitored closely postop and may need to be empirically placed on NPPV with a backup rate. Those patients already using NPPV should, at minimum, be using their NPPV. Supplemental O_2 should not be used without some form of ventilation. Lastly, mechanical cough augmentation devices can be helpful in preventing atelectasis and postop pneumonia. Mechanical cough augmentation devices are recommended for postop patients with Duchenne's muscular dystrophy with MEP <60 cm H_2O or PCF <270 L/min [66].

Specific Neuromuscular Conditions Commonly Associated with Respiratory Failure

Late-Onset–Adult-Onset Acid Maltase Deficiency

Late-onset–adult-onset acid maltase deficiency should be considered in adults who present with a chronic myopathy associated with early or disproportionate diaphragm weakness. Late-onset acid maltase deficiency is a lysosomal glycogen storage disorder caused by mutations in the gene that encodes α-glucosidase (GAA) whose deficiency results in accumulation of glycogen in lysosomal structures in muscle fibers and other tissues. Symptoms can begin in childhood or in adulthood and respiratory symptoms may be the initial presentation in a third of patients. Muscle enzymes can be mildly elevated but not uncommonly are normal. The EMG shows small myopathic motor units, and myotonic discharges in the paraspinal muscles. Muscle biopsy results are variable. In the classic case, there is positive staining for acid phosphatase vacuoles and increase in glycogen. Diagnosis is made by assay of GAA activity in dried blood spot and can be confirmed with a genetic test.

The distribution of weakness can be variable with a third presenting with respiratory weakness. Proximal and paraspinal weakness, difficulty with posture, and scapular winging should suggest this diagnosis, including those with floppy head syndrome and bent spine syndrome. The disorder has become the focus of heightened interest given the recent development of enzyme replacement therapy. Replacement therapy in infants prolongs survival and improves motor outcomes. Recent studies indicate that adults appear to receive a stabilizing benefit in an 18-month, randomized, placebo-controlled study of 90 patients. An increased walking distance and stabilization of pulmonary function were observed in the treated patients compared with those receiving placebo. In a study of enzyme replacement therapy in five older children ages 6–15 years who were treated for 3 years, there was improvement in muscle strength, and pulmonary function remained stable or improved slightly. No patients deteriorated in contrast to the natural history of the disease. Treatments were well tolerated [82–85].

Myasthenia Gravis

Myasthenia gravis (MG) is an autoimmune disorder of neuromuscular transmission involving the production of autoantibodies directed against the nicotinic acetylcholine receptor. Acetylcholine receptor antibodies are detectable in the serum of 80–90% of patients with MG. The prevalence of MG is about 1 in 10–20,000. Women are affected about twice as often as men. Symptoms may begin at virtually any age with a peak in women in the second and third decades, while the peak in men occurs in the fifth and sixth decades. Associated autoimmune diseases, such as rheumatoid arthritis, lupus, and pernicious anemia are present in about 5% of patients. Thyroid disease occurs in about 10%, often in association with antithyroid antibodies. About 10–15% of MG patients have a thymoma, while thymic lymphoid hyperplasia with proliferation of germinal centers occurs in 50–70% of cases. In most patients the cause of autoimmune MG is unknown. However, there are three iatrogenic causes for autoimmune MG. D-penicillamine (used in the treatment of Wilson's disease and rheumatoid arthritis) and alfa-interferon therapy are both capable of inducing MG. In addition, bone marrow transplantation is associated with the development of MG as part of the chronic graft versus host disease.

Clinical Features

The hallmark of myasthenia gravis is fluctuating or fatigable weakness. The presenting symptoms are ocular in half of all patients (25% of patients initially present with diplopia, 25% with ptosis), and by 1 month into the course of illness, 80% of patients have some degree of ocular involvement. Presenting symptoms are bulbar (dysarthria or dysphagia) in 10%, leg weakness (impaired walking) in 10%, and generalized weakness in 10%. Respiratory failure is the presenting symptom in

1% of cases. Patients usually complain of symptoms from focal muscle dysfunction, such as diplopia, ptosis, dysarthria, dysphagia, inability to work with arms raised over the head, or disturbance of gait. In contrast, patients with MG tend not to complain of "generalized weakness," "generalized fatigue," "sleepiness," or muscle pain. In the classic case, fluctuating weakness is worse with exercise and improved with rest. Symptoms tend to progress later in the day. Many different factors can precipitate or aggravate weakness, such as physical stress, emotional stress, infection, or exposure to medications that impair neuromuscular transmission (perioperative succinylcholine, aminoglycoside antibiotics, quinine, quinidine, botulinum toxin).

Diagnosis

The diagnosis is based on a history of fluctuating weakness with corroborating findings on examination. There are several different ways to validate or confirm the clinical diagnosis.

Edrophonium (Tensilon) Test

The most immediate and readily accessible confirmatory study is the edrophonium (Tensilon) test. To perform the test, choose one or two weak muscles to judge. Ptosis, dysconjugate gaze, and other cranial nerve deficits provide the most reliable endpoints. Use a setting where hypotension, syncope, or respiratory failure can be managed as patients occasionally decompensate during the test. If the patient has severe dyspnea, defer the test until the airway is secure. Start an IV. Have intravenous atropine 0.4 mg readily available in the event of bradycardia or extreme GI side effects. Edrophonium 10 mg (1 mL) is drawn up in a syringe and 1 mg (0.1 mL) should be given as a test dose while checking the patient's heart rate (to assure the patient is not supersensitive to the drug). If no untoward side effects occur after 1 min, another 3 mg is given. Many myasthenia gravis patients will show improved power within 30–60 s of giving the initial 4 mg dose at which point the test can be stopped. If after 1 min there is no improvement, give an additional 3 mg, and if there is still no response, 1 min later, give the final 3 mg. If the patient develops muscarinic symptoms or signs at any time during the test (sweating, salivation, GI symptoms), one can assume that enough edrophonium has been given to see improvement in strength and the test can be stopped. When a placebo effect or examiner bias is of concern, the test is performed in a double-blind placebo control fashion. The 1-mL control syringe contains either saline, 0.4-mg atropine, or 10-mg nicotinic acid. Improved strength from edrophonium lasts for just a few minutes. When improvement is clear-cut, then the test is positive. If the improvement is borderline, it is best to consider the test negative. The test can be repeated several times. The sensitivity of the edrophonium test is about 90%. The specificity is difficult to determine, as improvement following IV edrophonium has been reported in other neuromuscular diseases, including Lambert–Eaton syndrome, botulism, GBS, motor neuron disease, and lesions of the brainstem and cavernous sinus. That is the good news. The bad news is that edrophonium has been essentially taken off the market and unless stockpiled in your hospital may no longer be an option. So what is one supposed to do in place of the edrophonium test?

Neostigmine has a longer duration of effect and in selected patients may be an alternative cholinesterase inhibitor for diagnostic testing, especially in children. For the performance of a "neostigmine test," 0.04 mg/kg is given intramuscularly or 0.02 mg/kg intravenously (one time only). One can also perform an oral pyridostigmine test. Have the patient return for reexamination 60 min after the taking the pill. Pyridostigmine can also be given intravenously. The adult dose for diagnostic testing is 1 mg IV.

Acetylcholine Receptor Antibodies

The standard assay for receptor binding antibodies is an immunoprecipitation assay using human limb muscle for acetylcholine receptor antigen. In addition, assays for receptor modulating and blocking antibodies are available. Binding antibodies are present in about 80% of all myasthenia patients (50% of patients with pure ocular MG, 80% of those with mild generalized MG, 90% of patients with moderate to severe generalized

MG, and 70% of those in clinical remission). By also testing for modulating and blocking antibodies, the sensitivity improves to 90% overall. Specificity is outstanding with false positives exceedingly rare in reliable labs. If blood is sent to a reference lab, the test results are usually available within a week.

MuSK Antibodies

More recently 25–47% of patients seronegative for acetylcholine receptor antibodies have been shown to have muscle specific kinase (MuSK) antibodies. MuSK antibodies can now be measured by a commercially available immunoprecipitation assay. The clinical features of MuSK positive patients may differ from non-MuSK MG patients. MuSK antibody positive patients tend to be younger women (under age 40) and have lower likelihood of abnormal repetitive stimulation and edrophonium test results. Bulbar symptoms are significantly more common at onset of disease in MuSK antibody positive patients. MuSK antibodies may also be more commonly associated with patients having weakness of neck extensor, shoulders, or respiratory muscles.

EMG (Electrophysiological Testing)

Repetitive stimulation testing is widely available and has variable sensitivity depending on number and selection of muscles studied and various provocative maneuvers. However, in most labs, this technique has a sensitivity of about 50% in all patients with MG (lower in patients with mild or pure ocular disease). In general, the yield from repetitive stimulation is higher when testing muscle groups having clinically significant weakness. Single-fiber EMG is a highly specialized technique, usually available in major academic centers, with a sensitivity of about 90%. Abnormal single-fiber results are common in other neuromuscular disease and therefore the test must be used in the correct clinical context. The specificity of single-fiber EMG is an important issue in that mild abnormalities can clearly be present with a variety of other diseases of the motor unit including motor neuron disease, peripheral neuropathy, and myopathy. Disorders of neuromuscular transmission other than MG can have substantial abnormalities on SFEMG. In contrast, acetylcholine receptor antibodies (and MuSK antibodies) are not found in non-MG patients. In summary, the two highly sensitive laboratory studies are single-fiber EMG and acetylcholine receptor antibodies; nonetheless, neither test is 100% sensitive. Recent study of the added benefit of exercise on the presence of decrement has indicated that exercise increases the yield of diagnosis of MG by repetitive stimulation in only a small percent of patients. Thus, for most patients with suspected MG, repetitive stimulation at rest is sufficient.

Prognosis

Management of the patient with autoimmune MG requires understanding of the natural course of the disease. The long-term natural course of MG is not clearly established other than being highly variable. Several generalizations can be made. About half of MG patients present with ocular symptoms and by 1 month, 80% have eye findings. The presenting weakness is bulbar in 10%, limb in 10%, generalized in 10%, and respiratory in 1%. By 1 month, symptoms remain purely ocular in 40%, generalized in 40%, limited to the limbs in 10%, and limited to bulbar muscles in 10%. Weakness remains restricted to the ocular muscles on a long-term basis in about 15–20% (pure ocular MG). Most patients with initial ocular involvement tend to develop generalized weakness within the first year of the disease (90% of those who generalize do so within the initial 12 months). Maximal weakness occurs within the initial 3 years in 70% of patients. In the modem era death from MG is rare. Spontaneous long-lasting remission occurs in about 10–15%, usually in the first year or two of the disease. Most MG patients develop progression of clinical symptoms during the initial 2–3 years. However, progression is not uniform, as illustrated by 15–20% of patients whose symptoms remain purely ocular and those who have spontaneous remission.

Table 16.6 Cholinesterase inhibitors

	Unit dose	Average dose (adult)
Pyridostigmine bromide tablet (Mestinon)	60-mg tablet	30–60 mg every 4–6 h
Pyridostigmine bromide syrup	12 mg/mL	30–60 mg every 4–6 h
Pyridostigmine bromide Timespan (Mestinon Timespan)	180-mg tablet	1 tablet twice daily
Pyridostigmine bromide (parenteral)	5 mg/mL ampoules (1/30 of oral dose)	1–2 mg every 3–4 h
Neostigmine bromide (Prostigmin)	15-mg tablet	7.5–15 mg every 3–4 h
Neostigmine methylsulfate (parenteral)	0.25–1.0 mg/mL ampoules	0.5 mg IM, IV, or SC every 2–3 h
Children's dosing Edrophonium (Tensilon) Pyridostigmine bromide (Mestinon) Neostigmine methylsulfate (parenteral)	 Diagnosis: 0.1 mg/kg IV (or 0.15 mg/kg IM or SC, which prolongs the effect), preceded by a test dose of 0.01 mg/kg Treatment: oral dose is about 1.0 mg/kg every 4–6 h, as tablets or syrup (60 mg/5 mL) Diagnosis: 0.1 mg/kg/ IM or SC ×1 or 0.05 mg/kg/ IV ×1 Treatment: 0.01–0.04 mg/kg/dose IM, IV, or SC q 2–3 h prn	

Treatment

First-Line Therapy: Mestinon

Cholinesterase inhibitors (CEI) are safe, effective, and first-line therapy in all patients. Inhibition of acetylcholinesterase (AChE) reduces the hydrolysis of acetylcholine (ACh), increasing the accumulation of ACh at the nicotinic postsynaptic membrane. The CEIs used in MG bind reversibly (as opposed to organophosphate CEIs, which bind irreversibly) to AChE. These drugs cross the blood–brain barrier poorly and tend not to cause central nervous system side effects. Absorption from the gastrointestinal tract is inefficient and variable, with oral bioavailability of about 10%. Muscarinic autonomic side effects of gastrointestinal cramping, diarrhea, salivation, lacrimation, diaphoresis, and when severe, bradycardia may occur with all of the CEI preparations. A feared potential complication of excessive CEI use is skeletal muscle weakness (cholinergic weakness). Patients receiving parenteral CEI are at the greatest risk to have cholinergic weakness. It is uncommon for patients receiving oral CEI to develop significant cholinergic weakness even while experiencing muscarinic cholinergic side effects. Commonly available CEIs are summarized in Table 16.6.

Pyridostigmine (Mestinon) is the most widely used CEI for long-term oral therapy. Onset of effect is within 15–30 min of an oral dose, with peak effect within 1–2 h, and wearing off gradually at 3–4 h postdose. The starting dose is 30–60 mg three to four times per day depending on symptoms. Optimal benefit usually occurs with a dose of 60 mg every 4 h. Muscarinic cholinergic side effects are common with larger doses. Occasional patients require and tolerate over 1,000 mg/day, dosing as frequently as every 2–3 h. Patients with significant bulbar weakness will often time their dose about 1 h before meals in order to maximize chewing and swallowing. Of all the CEI preparations, pyridostigmine has the least muscarinic side effects. Pyridostigmine may be used in a number of alternative forms to the 60-mg tablet. The syrup may be necessary for children or for patients with difficulty swallowing pills. Sustained release pyridostigmine 180 mg (Mestinon Timespan) is sometimes preferred for nighttime use. Unpredictable release and absorption limit its use. Patients with severe dysphagia or those undergoing surgical procedures may need parenteral CEI. Intravenous pyridostigmine should be given at about 1/30 of the oral dose. Neostigmine (prostigmine) has a slightly shorter duration of action and slightly greater muscarinic side effects.

For patients with intolerable muscarinic side effects at CEI doses required for optimal power,

a concomitant anticholinergic drug such as atropine sulfate (0.4–0.5 mg po) or glycopyrrolate (Robinul) (1–2 mg po) on an as needed basis or with each dose of CEI may be helpful. Patients with mild disease can often be managed adequately with CEIs. However, patients with moderate, severe, or progressive disease will usually require more effective therapy.

Thymectomy: For Whom, What Type, and What to Tell the Patient to Expect?

The association of the thymus gland with myasthenia gravis was first noted around 1900 and thymectomy has become standard therapy for over 50 years. Prospective controlled trials have not been performed for thymectomy, although such a trial is currently in the planning stage. Nonetheless, thymectomy is generally recommended for patients with moderate to severe MG especially those inadequately controlled on CEI, and those under the age of 55 years. All patients with suspected thymoma undergo surgery. About 75% of MG patients appear to benefit from thymectomy. Patients may improve or simply stabilize. For unclear reasons, the onset of improvement tends to be delayed by a year or two in most patients. For some patients improvement occurs 5–10 years after surgery. The majority of surgeons use the transsternal approach for thymectomy with the goal of complete removal of the gland. The limited transcervical approach has been largely abandoned due to the likelihood of incomplete gland removal. Many experts recommend a "maximal thymectomy" in order to ensure complete removal. The procedure involves a combined transsternal–transcervical exposure with en block removal of the thymus. If thymectomy is to be performed, choose an experienced surgeon, anesthesiologist, and medical center with a good track record and insist that the entire gland is removed.

Which patients do not undergo thymectomy? Patients with very mild or trivial symptoms do not have surgery. Most patients with pure ocular MG do not undergo thymectomy even though there has been some reported benefit in selected patients. Thymectomy is often avoided in children due to the theoretical possibility of impairing the developing immune system. However, reports of thymectomy in children as young as 2–3 years of age have shown favorable results without adverse effects on the immune system. Thymectomy has been largely discouraged in patients over age 55 because of expected increased morbidity, latency of clinical benefit, and frequent observation of an atrophic, involuted gland. Nonetheless there are older patients reported to benefit from thymectomy. Major complications from thymectomy are uncommon so long as the surgery is performed at an experienced center with anesthesiologists and neurologists familiar with the disease and perioperative management of MG patents.

Common although less serious aspects of thymectomy include postoperative chest pain (which may last several weeks), a 4- to 6-week convalescence period, and cosmetically displeasing incisional scar.

In an effort to clarify the benefit of thymectomy in the treatment of MG, the international thymectomy trial is past the halfway point with enrollment of patients. In this seminal study, patients are randomized to thymectomy/prednisone or to no thymectomy/prednisone and their prednisone dose is adjusted over time as needed to establish optimal control (dosage adjusted by a blinded evaluator). After 3 years, the two groups will be compared for reduction in myasthenic weakness, and the total amount of prednisone used in the thymectomy group will be compared with that required in the no thymectomy group as primary outcome measures.

Corticosteroids

There are no controlled trials documenting the benefit of corticosteroids in MG. However, nearly all authorities have personal experience attesting to the virtues (and complications) of corticosteroid use in MG patients. In general, corticosteroids are used in patients with moderate to severe, disabling symptoms which are refractory to CEI. Patients are commonly hospitalized to initiate therapy due to the risk of early exacerbation. Opinions differ regarding the best method of administration. For patients with severe MG it is best to begin with high-dose daily therapy of 60–80 mg/day orally. Early

exacerbation occurs in about half of patients usually within the first few days of therapy and typically lasts 3 or 4 days. In 10% of cases, the exacerbation is severe requiring mechanical ventilation or a feeding tube (thus the need to initiate therapy in the hospital). Overall about 80% of patient show a favorable response to steroids (with 30% attaining remission and 50% marked improvement). Mild to moderate improvement occurs in 15%, and 5% have no response. Improvement begins as early as 12 h and as late as 60 days after beginning prednisone, but usually the patient begins to improve within the first week or two. Improvement is gradual, with marked improvement occurring at a mean of 3 months, and maximal improvement at a mean of 9 months. Of those patients having a favorable response, most maintain their improvement with gradual dosage reduction at a rate of 10 mg every 1–2 months. More rapid reduction is usually associated with a flare-up of the disease. While many patients can eventually be weaned off of steroids and maintain their response, the majority cannot. They require a minimum dose (5–30 mg alternate day) in order to maintain their improvement. Complications of long-term high-dose prednisone therapy are substantial, including cushingoid appearance, hypertension, osteoporosis, cataracts, aseptic necrosis, and the other well-known complications of chronic steroid therapy. Older patients tend to respond more favorably to prednisone. An alternative prednisone regimen involves low-dose alternate day, gradually increasing schedule in an attempt to avoid the early exacerbation. Patients receive prednisone 25 mg on alternate days with an increase of 12.5 mg every third dose (about every 5th day) to a maximum dose of 100 mg on alternate days or until sufficient improvement occurs. Clinical improvement usually begins within 1 month of treatment. The frequency and severity of early exacerbation is less than that associated with high-dose daily regimens. High-dose intravenous methylprednisolone (1,000 mg IV daily for 3–5 days) can provide improvement within 1–2 weeks, but the clinical improvement is temporary.

Alternative Immunosuppressive Drug Therapy

Mycophenolate mofetil (CellCept) is a purine inhibitor widely used in recent years for the treatment of MG. While prospective controlled trials are underway, the anecdotal uncontrolled experience would suggest that about 75% of MG patients benefit from the drug with the typical onset of improvement within 2–3 months. The drug is in general well tolerated. Typically begin with 250–500 mg po bid and over 2–4 weeks increase the dose to 1,000 mg po bid. There are two recently completed prospective controlled trials of CellCept in MG that have demonstrated no clear-cut benefit. In the first study, an investigator-initiated trial, 80 patients were randomly assigned to receive prednisone plus CellCept or prednisone plus placebo. After 3 months, improvement was measured by the change from baseline QMG score with a difference of 3 points clinically significant. In both groups, there was improvement and at 3 months there was no significant difference in the mean QMG score. The second study involved 176 patients who were already taking prednisone. They were randomly assigned to prednisone plus CellCept or prednisone plus placebo for 36 weeks. On evaluation at 36 weeks, there was no difference between the two treatment groups. While the two studies did not demonstrate a benefit from CellCept, it is important to look carefully at all of the data, consider the type of patients studied, the design of the studies, the impact of prednisone and Mestinon, duration of treatment, and many other factors that could influence the results. In current clinical practice there are differing views on the use of CellCept and other immunosuppressive medications for treatment of MG. Patients with questions about their own use of CellCept are advised to discuss their management with their individual physician. Many clinicians feel strongly that CellCept is an excellent drug for the treatment of myasthenia gravis even though these two studies did not demonstrate a benefit. Concerns have also been raised over the observations of patients taking mycophenolate mofetil and subsequently developing PML. While these have not been MG

patients, the concern is understandable. Further studies are expected [86, 87].

Azathioprine (Imuran) is a cytotoxic purine analog with extensive use in MG (but largely uncontrolled and retrospective). The starting dose is 50 mg po daily, with CBC and liver function tests weekly in the beginning. If the drug is tolerated and if the blood work is stable, the dose is increased by 50 mg every 1–2 weeks aiming for a total daily dose of 2–3 mg/kg/day (about 150 mg/day in the average size adult). When azathioprine is first started, about 15% of patients will have intolerable GI side effects (nausea, anorexia, abdominal discomfort) sometime associated with fever, leading to discontinuation. Bone marrow suppression with relative leukopenia (WBC 2,500–4,000) occurs in 25% of patients but is usually not significant. If the WBC drops below 2,500 or the absolute granulocyte count goes below 1,000 the drug is stopped (and the abnormalities usually resolve). Macrocytosis is common and of unclear clinical significance. Liver enzymes elevate in 5–10%, but this is usually reversible and severe hepatic toxicity occurs in only about 1%. Infection occurs in about 5%. There is a theoretical risk of malignancy (based on observations in organ transplant patients), but this increased risk has not been clearly established in the MG patient population. About half of MG patients improve on azathioprine with onset about 4–8 months into treatment. Maximal improvement takes about 12 months. Relapse after discontinuation of azathioprine occurs in over half of patients, usually within 1 year.

Cyclosporine is used in patients with severe MG who cannot be adequately managed with corticosteroids or azathioprine. The starting dose is 3–5 mg/kg/day given in two divided doses. Cyclosporine blood levels should be measured monthly (aiming for a level of 200–300) along with electrolytes, magnesium, and renal function. In general, serum creatinine should not exceed one and one half times the pretreatment level. Blood should be sampled before the morning dose is taken. Over half of patients improve on cyclosporine. The onset of clinical improvement occurs about 1–2 months after beginning therapy and maximal improvement occurs at about 3–4 months. Side effects include renal toxicity and hypertension. Nonsteroidal anti-inflammatory drugs and potassium-sparing diuretics are among the list of drugs that should be avoided while on cyclosporine. In patients on corticosteroids, the addition of cyclosporine can lead to a reduction in steroid dosage, although it is usually not possible to discontinue prednisone.

Methotrexate has been used is selected patients for decades with clinical response the subject of sporadic anecdotal reports. Currently a large prospective multicenter study of methotrexate in myasthenia gravis is under way to clarify its value in treatment.

Tacrolimus has reported to be beneficial in several series and in some parts of the world is among the more commonly prescribed immunosuppressive agents.

Rituximab has been reported to be effective in treating MG in selected patients. The anecdotal reports tend to involve relatively refractory patients who have done poorly with alternative treatment options. The anecdotal reports of rituximab benefits in MuSK patients are particularly notable given the disproportionate tendency for such patients to be refractory to many other immunosuppressive agents.

Plasma Exchange

Plasma exchange (plasmapheresis) removes acetylcholine receptor antibodies and results in rapid clinical improvement. The standard course involves removal of 2–3 L of plasma every other day or three times per week until the patient improves (usually a total of three to five exchanges). Improvement begins after the first few exchanges and reaches maximum within 2–3 weeks. The improvement is moderate to marked in nearly all patients, but usually wears off after 4–8 weeks due to the reaccumulation of pathogenic antibodies. Vascular access may require

placement of a central line. Complications include hypotension, bradycardia, electrolyte imbalance, hemolysis, infection, and access problems (such as pneumothorax from placement of a central line.) Indications for plasma exchange include any patient in whom a rapid temporary clinical improvement is needed. There are occasional patients who have severe dysfunction and do poorly on medication such that weekly plasma exchange eventually becomes the mainstay of their long-term management.

High-Dose IVIg

High-dose intravenous immunoglobulin (IVIg) administration is associated with rapid improvement in MG symptoms in a time frame similar to plasma exchange. The mechanism is unclear but may relate to downregulation of acetylcholine receptor antibody production or to the effect of anti-idiotype antibodies. The usual protocol is 2 g/kg administered over 5 consecutive days (0.4 g/kg/day). Different IVIg preparations are administered IV at different rates (contact the pharmacy for guidelines). The majority of MG patients improve, usually within 1 week of starting IVIg. The degree of response is variable and the duration of response is limited similar to plasma exchange, to about 4–8 weeks. Complications include fever, chills, and headache, which respond to slowing down the rate of the infusion, and giving diphenhydramine. Occasional cases of aseptic meningitis, renal failure, nephrotic syndrome, and stroke have been reported. Also, patients with selective IgA deficiency can have anaphylaxis best avoided by screening for IgA deficiency ahead of time. The treatment is relatively expensive, comparable to plasma exchange. In a recent blinded, randomized, placebo-controlled trial, 51 patients with severe MG weakness were assigned to receive an infusion with 2 g/kg of intravenous immunoglobulin or an equivalent volume of 5% intravenous dextrose in water. In patients treated with intravenous immunoglobulin, a clinically meaningful improvement in QMG score was observed at day 14 and persisted at day 28. Overall improvement in QMG score at day 14 was 2.54 units in the intravenous immunoglobulin group compared with 0.89 in the placebo group, and at day 28, improvement was 3.00 units vs. 1.19, respectively. The greatest improvement (of approximately 4 points) occurred in patients with more severe disease, as defined by a QMG score greater than 10.5. The study provides level 1 evidence for the effectiveness of IVIg in patients with worsening weakness due to myasthenia gravis [88]. Over the past few years there has been increasing interest in the subcutaneous route of administration of immunoglobulin. Occasional patients do poorly on alternative therapy and rely on scheduled periodic IVIg for their long-term maintenance therapy.

General Guidelines for Management

1. Be certain of the diagnosis.
2. Patient education. Provide the patient with information about the natural course of the disease, including the variable and somewhat unpredictable course. Briefly review the treatment options outlined above pointing out effectiveness, time course of improvement, duration of response, and complications. Provide the patient with educational pamphlets prepared by the Myasthenia Gravis Foundation or the Muscular Dystrophy Association.
3. When to hospitalize the patient. Patients with severe MG can deteriorate rapidly over a period of hours. Therefore, those having dyspnea should be hospitalized immediately in a constant observation or intensive care setting. Patients with moderate or severe dysphagia, weight loss, as well as those with rapidly progressive or severe weakness should be admitted urgently. This will allow close monitoring and early intervention in the case of respiratory failure, and will also expedite the diagnostic workup and initiation of therapy.
4. Myasthenic crisis (Table 16.7) is a medical emergency characterized by respiratory failure from diaphragm weakness or severe oropharyngeal weakness leading to aspiration. Crisis can occur in the setting of surgery (postop), acute infection, or following rapid withdrawal of corticosteroids, although some

Table 16.7 The acutely deteriorating myasthenic patient

Myasthenic crisis
Respiratory distress
Respiratory arrest
Cyanosis
Increased pulse and blood pressure
Diaphoresis
Poor cough
Inability to handle oral secretions
Dysphagia
Weakness
Improves with edrophonium
Cholinergic crisis
Abdominal cramps
Diarrhea
Nausea and vomiting
Excessive secretions
Miosis
Fasciculations
Diaphoresis
Weakness
Worse with edrophonium

patients have no precipitating factors. Patients should be placed in an ICU setting and have FVC checked every 2 h. Changes in ABGs occur relatively late in neuromuscular respiratory failure. There should a low threshold for intubation and mechanical ventilation. Criteria for intubation include a drop in the FVC below 15 mL/kg (or below 1 L in an average sized adult), severe aspiration from oropharyngeal weakness, or labored breathing regardless of the measurements. If the diagnosis is not clear-cut, it is advisable to secure the airway with intubation, stabilize ventilation, and only then address the question of the underlying diagnosis. If the patient has been taking CEI the drug should be temporarily discontinued in order to rule out the possibility of "cholinergic crisis."

5. Screen for and correct any underlying medical problems such as systemic infection, metabolic problems (i.e., diabetes), and thyroid disease. Hypo- or hyperthyroidism can exacerbate MG.
6. Drugs to avoid in MG. Avoid using D-penicillamine, alfa-interferon, chloroquine, quinine, quinidine, procainamide, and botulinum toxin. Aminoglycoside antibiotics should be avoided unless needed for a life-threatening infection. Fluoroquinolones (ciprofloxacin) and erythromycin have significant neuromuscular blocking effects. Telithromycin (Ketek), a ketolide antibiotic, has been reported to cause life-threatening weakness in patients with MG and should not be used. Neuromuscular blocking drugs, such as pancuronium and D-tubocurarine, can produce marked and prolonged paralysis in MG patients. Depolarizing drugs, such as succinylcholine, can also have a prolonged effect and should be used by a skilled anesthesiologist who is well aware of the patient's MG. Recent reports suggest that in some patients statin drugs may aggravate MG [89].

Guidelines for Specific Therapies

Treatment must be individualized. Mild diplopia and ptosis may not be disabling for some patients, but for a pilot or neurosurgeon mild intermittent diplopia may be critical. In similar fashion, some patients may tolerate side effects better than others:

1. Mild or trivial weakness, either localized or generalized, should be managed with a cholinesterase inhibitor.
2. Moderate to marked weakness, localized or generalized, should initially be managed with a cholinesterase inhibitor. Even if symptoms are adequately controlled, patients under age 55 should undergo thymectomy early in the course of the disease (within the first year). In older patients, thymectomy is usually not performed unless the patient is thought to have a thymoma. Thymectomy is performed at an experienced center with the clear intent of complete removal of the gland. All patients with suspected thymoma (by chest scan) should have thymectomy, even if their myasthenic symptoms are mild. Unless a thymoma is suspected, patients with pure ocular disease are usually not treated with thymectomy.
3. If symptoms are inadequately controlled on cholinesterase inhibitors, immunosuppression is used. High-dose corticosteroid therapy is the most predictable and effective long-term option. If patients have severe, rapidly progressive, or life-threatening symptoms, the decision to start corticosteroids is clear-cut.

Patients with disabling but stable symptoms may instead receive azathioprine or mycophenolate mofetil especially if there are particular concerns about using corticosteroids (i.e., the patient is already overweight, diabetic, or cosmetic concerns). Those patients who respond poorly or have unacceptable complications on steroids are started on alternative immunosuppressive agents.

4. Plasma exchange or IVIg are indicated in:
   (a) Rapidly progressive, life-threatening, and impending myasthenic crisis or actual crisis, particularly if prolonged intubation with mechanical ventilation is judged hazardous
   (b) Preoperative stabilization of MG (such as prior to thymectomy or other elective surgery) in poorly controlled patients
   (c) Disabling MG refractory to other therapies.
5. If these options fail, then consider usage of cyclosporine, tacrolimus, methotrexate, and rituximab.
6. Also, as some patients do poorly on the drugs above, and others cannot wait for 3, 6, or 9 months for a clinical response, there is the option to use IVIg for more rapid improvement/stabilization as well as for long-term maintenance therapy.
7. If the patient remains poorly controlled despite treatment as above, then perform a repeat chest CT scan looking for residual thymus. Some patients improve after "repeat thymectomy." Check for other medical problems (diabetes, thyroid disease, infection, and coexisting autoimmune diseases).
8. Referral to a neurologist or center specializing in neuromuscular disease is advised for all patients with suspected MG and can be particularly important for complicated or refractory patients.

Miscellaneous Myasthenia Issues

Transient neonatal myasthenia occurs in 10–15% of babies born to mothers with autoimmune MG. Within the first few days after delivery, the baby has a weak cry or suck, appears floppy, and, on occasion, requires mechanical ventilation. The condition is caused by maternal antibodies that cross the placenta late in pregnancy. As these maternal antibodies are replaced by the baby's own antibodies, the symptoms gradually disappear, usually within a few weeks, and the baby is normal thereafter. Infants with severe weakness are treated with oral pyridostigmine 1–2 mg/kg every 4 h.

Congenital myasthenia represents a group of rare hereditary disorders of the neuromuscular junction. Patients tend to have lifelong relatively stable symptoms of generalized fatigable weakness. These disorders are nonimmunologic, without acetylcholine receptor antibodies, and therefore, patients do not respond to immune therapy (steroids, thymectomy, and plasma exchange). Most of these patients improve on cholinesterase inhibitors. While there are many established subtypes of congenital myasthenia several are worth noting due in part to specific therapeutic implications. The *fast channel congenital myasthenic syndrome* tends to be static or slowly progressive, but usually very responsive to combination therapy with 3,4-diaminopyridine (enhances release of acetylcholine) and pyridostigmine (reduces metabolism of acetylcholine). In *congenital slow channel myasthenic syndrome* the disease typically worsens over years as the endplate myopathy progresses. Although cholinesterase inhibitors typically worsen symptoms, quinidine and fluoxetine, which reduce the duration of acetylcholine receptor channel openings, are both effective treatments for slow channel syndrome. The *congenital myasthenic syndrome associated with acetylcholine receptor deficiency* tends to be relatively nonprogressive and may even improve slightly as the patient ages. The disorder typically responds to symptomatic therapy with pyridostigmine and/or 3,4-diaminopyridine. Ephedrine produces benefit in some cases. Patients with *congenital endplate acetylcholinesterase deficiency* usually present in infancy or early childhood with generalized weakness, underdevelopment of muscles, slowed pupillary responses to light and either no response or worsening with cholinesterase inhibitors. No effective long treatment has been described for congenital endplate acetylcholinesterase deficiency.

Lambert–Eaton's Syndrome

Lambert–Eaton's syndrome (LES) (the myasthenic syndrome) is a presynaptic disease characterized by chronic fluctuating weakness of proximal limb muscles. Symptoms include difficulty walking, climbing stairs, or rising from a chair (Table 16.8). In LES there may be some improvement in power with sustained or repeated exercise. In contrast, the myasthenia gravis ptosis, diplopia, dysphagia, and respiratory failure are far less common. In addition, LES patients often complain of myalgias, muscle stiffness of the back and legs, distal paresthesias, metallic taste, dry mouth, impotence, and other autonomic symptoms of muscarinic cholinergic insufficiency. Lambert–Eaton syndrome is rare compared to myasthenia gravis, which is about 100 times more common. About half of LES patients have an underlying malignancy, which is usually small cell carcinoma of the lung. In patients without malignancy, LES is an autoimmune disease and can be associated with other autoimmune phenomenon. In general, patients with Lambert–Eaton syndrome over age 40 are more likely to be men and have an associated malignancy whereas younger patients are more likely to be women and have no malignancy. Lambert–Eaton syndrome symptoms can precede detection of the malignancy by 1–2 years.

The examination typically shows proximal lower extremity weakness, although the objective bedside assessment may suggest relatively mild weakness relative to the patient's history. The muscle stretch reflexes are absent. On testing sustained maximal grip there is a gradual increase in power over the initial 2–3 s (Lambert's sign).

The diagnosis is confirmed with EMG studies which typically show low amplitude of the CMAPs and a decrement to slow rates or repetitive stimulation. Following brief exercise, there is marked facilitation of the CMAP amplitude. At high rates of repetitive stimulation, there may be an incremental response. Single-fiber EMG is markedly abnormal in virtually all patients with LES. The pathogenesis involves autoantibodies directed against voltage-gated calcium channels at cholinergic nerve terminals. These IgG antibodies also inhibit cholinergic synapses of the autonomic nervous system. Antibodies to voltage-gated calcium channels are present in serum in over 75% of LES patients, providing another important diagnostic test. In patients with associated malignancy, successful treatment of the tumor can lead to improvement in the LES symptoms. Symptomatic improvement in neuromuscular transmission may occur with the use of cholinesterase inhibitors, such as pyridostigmine. Guanidine has shown some benefit but its use has been limited by bone marrow, renal, and hepatic toxicity. Guanidine increases the release of ACh by increasing the duration of the action potential at the motor nerve terminal. 3,4-diaminopyridine (DAP) increases ACh release by blocking voltage-dependent potassium conductance and thereby prolonging depolarization at the nerve terminal and enhancing the voltage-dependent calcium influx. 3,4-DAP has been shown to clearly improve symptoms in most patients with LES with relatively mild toxicity and is becoming increasingly available, such that it represents first-line symptomatic therapy for LES. The typical beginning dose is 10 mg every 4–6 h with gradual increase as needed up to a maximum of 100 mg/day.

Table 16.8 Lambert–Eaton's syndrome (LES)

Symptoms
Proximal limb weakness
Legs > arms
Fatigue or fluctuating symptoms
Difficulty rising from a sitting position, climbing stairs
Metallic taste in mouth
Autonomic dysfunction
Dry mouth
Constipation
Blurred vision
Impaired sweating
Signs
Proximal limb weakness
Legs > arms
Weakness on exam is less compared to patient's level of disability
Hypoactive or absent muscle stretch reflexes
Lambert's sign (grip becomes more powerful over several seconds)

Immunosuppressive therapy is used in patients with disabling symptoms. Long-term high-dose corticosteroids, plasma exchange, and IVIg have all been used with moderate success. In general, the use of these therapies should be tailored to the severity of patient's symptoms.

Amyotrophic Lateral Sclerosis

As most ALS patients die from complications of respiratory failure, the clinician should anticipate the signs and symptoms of hypoventilation. Whether the goal is prolonged survival or maximal comfort or both, the management of respiratory failure in the ALS patient should be a high priority. Often the earliest signs of respiratory weakness are those associated with disturbed sleep. Daytime spirometry and blood gases may appear stable, and yet at night the patient may experience severe hypoventilation. In general, the pCO_2 will not begin to rise until the FVC falls below 50% of predicted. Early on the blood gas may show mild hypoxia and hypocapnia as the patient hyperventilates to maintain oxygenation. As respiratory function deteriorates, the patient develops CO_2 retention from hypoventilation, and the serum bicarbonate levels become elevated as compensation for the respiratory acidosis. Significant hypercapnia typically develops when the FVC is <30% of predicted, at which time the patient is at major risk for acute respiratory decompensation. As the FVC falls to 50–60%, the ALS patient begins to develop symptoms of hypoventilation, and the use of NPPV will improve symptoms (quality of life) as well as prolong survival.

ALS Pitfall Scenario

An ALS patient has chronic dyspnea due to diaphragm weakness. In an effort to provide maximum comfort, she is given supplemental oxygen. Over the next hour the patient appears much more comfortable and less short of breath. Two hours later she appears more peaceful and is finally able to go to sleep. Several hours later she has a respiratory arrest and dies. *Comment*: The problem here is that the patient with chronic hypoventilation may have a chronic elevation of pCO_2, leading to "hypoxic drive" of respiration. The supplemental oxygen raises the pO_2 and the patient loses their "hypoxic drive." Therefore the patient further hypoventilates leading to increasing levels of CO_2. The patient appears more comfortable, in part because of the sedating effects of hypercapnia. Such sedation becomes increasingly profound, and over the next few hours the patient follows a vicious cycle of increased sedation leading to reduced ventilation, which in turn raises the pCO_2 even further producing increasing sedation and ultimately a respiratory arrest. The solution is to utilize NPPV prior to adding the supplemental oxygen. Also, starting with lower concentrations of supplemental oxygen may be prudent.

Botulism

Consumption of sausage spoiled by *Clostridium botulinum* resulted in an outbreak of a paralytic illness in the 1700s in Germany, leading to the name botulism, derived from the Latin term for sausage, "botulus." Botulinum toxin blocks ACh release at the presynaptic motor nerve terminal, and causes dysautonomia by blocking muscarinic autonomic cholinergic function as well. The intracellular target of botulinum toxin appears to be a protein of the ACh vesicle membrane. The toxin is a zinc-dependent protease that cleaves protein components of the neuroexocytosis apparatus.

Classic Botulism

Classic botulism occurs after ingestion of food contaminated by botulinum toxin. Eight different toxins have been identified, but disease in humans is caused by A, B, and E. Type E is associated with contaminated seafood. All types produce a similar clinical picture, although type A may produce more severe and enduring symptoms. In all three types, the condition is potentially fatal. Most cases result from ingestion of bottled or canned foods that have not been properly sterilized during preparation, especially "home canned foods." Today's tomatoes used in home canning may have a lower acid content as compared to the "good old days" and therefore may be more vulnerable for contamination. Foods cooked on an

outdoor grill and then wrapped in foil for a day or two, creating an anaerobic environment, can lead to toxin production. Home-bottled oils and honey may be contaminated.

Clinical Features

Clinical features begin 12–48 h after ingestion of tainted food. Bulbar symptoms including diplopia, ptosis, blurred vision, dysarthria, and dysphagia occur initially, and are followed by weakness in the upper limbs and then in the lower limbs. In contrast to the typical patient with GBS, botulism is sometimes said to produce an acute "descending paralysis." Severe cases result in respiratory failure requiring mechanical ventilation. Botulism produces autonomic dysfunction, including constipation, ileus, dry mouth, and dilated pupils (note: some of these signs are seen in most but not all patients; normal pupils do not "rule out" the diagnosis of botulism).

Diagnosis

The compound motor action potential (CMAP) amplitudes are typically low on the motor NCS. Repetitive stimulation studies before and following exercise may show a decrement to low rates of repetitive stimulation and postexercise facilitation of the CMAP amplitude. Send both stool and serum specimens to the lab for detection of the toxin. The specimen is injected into the peritoneum of a mouse, while a neutralized or inactivated specimen is injected as the control. If the mouse becomes paralyzed and dies, the diagnosis is botulism. Toxin is found in blood samples 30–40% of the time, while stool samples have a somewhat higher yield (thus the need to send both). Newer PCR tests for the organism have been used to screen for the bacteria in food.

Management

Management involves placement of the patient in the intensive care unit and assiduous monitoring of pulmonary function every few hours. When the FVC falls below 15 mL/kg or below 1 L, or if the patient appears to be having respiratory difficulty, intubation and mechanical ventilation are necessary. There is a trivalent botulinum antitoxin, but its use is controversial, in part because of adverse side effects that occur in about 20% of patients. There is some evidence that the antitoxin shortens the course of the illness, especially that associated with type E. If the diagnosis is made early, it is reasonable to treat with antitoxin.

Clinical Course

With aggressive support, the overall mortality remains about 5–10%, usually the result of respiratory or septic complications. The other patients improve over a period of several weeks to several months. In those who survive, the eventual level of recovery is usually near complete. Several years after the illness, some patients have subjective fatigue and autonomic symptoms, including constipation, impotence, and dry mouth. Clinical recovery results from brisk sprouting of new motor axons from the nerve terminal with reinnervation of denervated muscle fibers.

Infant Botulism

Infant botulism is probably the most frequent form of botulism. The infant ingests the spores of *C. botulinum*, which lodge in the intestinal tract, germinate there, and produce botulinum toxin in the gut. Honey has often been implicated as the contaminated food in infant disease. In adults, the small amount of *C. botulinum* in honey appears inadequate to colonize the GI tract. The typical presentation is an infant between the ages of 6 weeks and 6 months of age who exhibits generalized weakness and constipation. The weakness may start in the cranial muscles and then descend, causing a weak suck, a poor cry, and reduced spontaneous movement. The cranial muscles are weak, with poor extraocular movements, reduced gag reflex, and drooling. Finding *C. botulinum* in feces validates the diagnosis. The toxin is usually not detectable in the serum. EMG studies are helpful in the diagnosis in 80–90% of cases. Infantile botulism can range from mild to severe. Management centers on observation and general support (including respiratory stability). The recovery is usually excellent and runs a course of several weeks to several months.

Table 16.9 Hypokalemic periodic paralysis

"Primary"—hereditary (autosomal dominant)
Genetic defect on chromosome 1—gene code for the dihydropyridine receptor
Presents in teenage years or in 20s
Upon awakening the patient is weak (can be mild or quadriplegia)
Limbs are hypotonic
Muscle stretch reflexes are absent
Cranial and respiratory muscle are usually spared
Serum potassium is low during the attack
Recovery occurs gradually over several hours
Precipitating factors include physical or emotional stress, high carbohydrate load
Most patients recover completely from an acute attack of paralysis, but some patients acquire mild fixed proximal weakness after many years of attacks
Preferred treatment of the hypokalemia 0.25 mEq/kg potassium chloride by mouth—in an unsweetened 10–25% solution—may repeat every 30 min until strength returns
Forms of secondary hypokalemic periodic paralysis:
Urinary or gastrointestinal loss of potassium
Primary hyperaldosteronism
Thiazide diuretic therapy
Excessive mineralocorticoid therapy for Addison's disease
Laxative abuse
Prolonged GI suction
Prolonged vomiting
Sprue
Villous adenoma of the rectum

Wound Botulism

Wound botulism occurs when toxin is produced from *C. botulinum* infection of a wound. The symptoms are similar to those of classic botulism except that the onset may be delayed for up to 2 weeks after contamination of the wound. The diagnosis is supported by EMG studies, demonstration of toxin in the patient's blood or finding the organism in the patient's wound. Wounds at risk for botulism include direct trauma, surgical wounds, and wounds associated with drug use (such as intravenous and intranasal cocaine).

Hypokalemic Periodic Paralysis

Hypokalemic periodic paralysis should be considered in the differential diagnosis of patients presenting with acute quadriparesis. The majority of such patients do not experience significant respiratory failure (Table 16.9).

Thyrotoxic Periodic Paralysis

Screen every patient with hypokalemic periodic paralysis for hyperthyroidism. Thyrotoxic periodic paralysis (TPP) is more common in Asians. Even though hyperthyroidism is more common in women than men, TPP is 70 times more common in men than women. Often, they do not have the typical systemic features of hyperthyroidism (they look clinically euthyroid). The disorder is usually sporadic (there is no family history) and the attacks stop when the patient becomes euthyroid.

Tick Paralysis

Clinical Features

Tick paralysis is one of the eight most common tick-mediated diseases. While it can affect a variety of species and any age group, it is most often reported in children. Usually the tick bite occurs 5–7 days before the onset of symptoms. The female tick then feeds, becomes engorged (such engorgement is facilitated by mating with the male tick), eggs become fertilized, and the female tick produces a neurotoxin—often referred to as ixobotoxin. The natural course of the tick encounter is that engorgement of the female tick reaches an end point at which point the female tick releases and eventually deposits it eggs. Children

tend to present with a day or two of progressive paresthesias and leg weakness with a tendency to fall. Usually, there is no fever. Over the next day or two the weakness tends to ascend and involve axial as well as limb muscles. There is truncal instability. The patient has difficulty with sitting, cannot walk, and becomes areflexic. As the disease progresses over the next day or two the patient may develop bulbar weakness and involvement of respiratory muscles. Some patients appear encephalopathic. The initial erroneous diagnosis is often GBS.

Diagnostic Studies

One of the best diagnostic tests in the literature is an electroencephalogram, in that an astute EEG technician may first spot the tick in the scalp while placing the electrodes. The NCS may suggest a peripheral neuropathy with prolonged distal latencies on the motor NCS, reduced nerve conduction velocity, and some reduction in amplitude of the sensory and motor responses. Repetitive stimulation studies are often unhelpful.

Treatment

If a tick is detected and removed (and usually it is in the hair or scalp) patients typically demonstrate dramatic resolution of their weakness over hours to several days. Otherwise, treatment involves general intensive care monitoring and support.

Subtypes of Tick Paralysis

In Australia the *Ixodes holocyclus* tick produces a toxin which seems to act similar to botulinum toxin in impairing the release of acetylcholine at motor nerve terminals. Patients in Australia with exposure to this tick classically have a more severe and fulminant paralytic illness than those exposed to the North American ticks. In addition, over the first 1–2 days after removal of the tick, clinical symptoms often become more pronounced, and the clinical recovery tends to be slower. In Australia it is generally recommended that *Ixodes holocyclus* antitoxin be given to the patient prior to removing the tick, and that patients be monitored for an extended period of time following tick removal.

In North America *Dermacentor* sp. ticks (*Dermacentor andersoni*, the North American wood tick) and *Dermacentor variabilis* (the common dog tick) are those that of concern for causing paralysis in adults, even though many other tick species can cause tick paralysis in animals. The *Dermacentor* sp. ticks are fairly easy to spot when they are engorged. Tick paralysis is somewhat more common in the spring and summer in the southeast and northwestern United States.

Conclusion

Neuromuscular disorders can present with acute respiratory failure either as the presenting symptom or as a complication of the known neuromuscular disorder [90]. However, patients with neuromuscular disorders can also present with other common causes of acute respiratory distress, e.g., PE. Therefore, an accurate diagnosis of respiratory failure is extremely important in initiating treatment. The method of ventilation should be determined based on the severity of respiratory insufficiency or failure, type of neuromuscular disease, and patient's wishes. The decision to intubate should be done early before acute respiratory arrest, mental status changes, or cardiac abnormalities develop. Patients who do not acutely need intubation should be monitored extremely vigilantly. Diagnosis of the neuromuscular disorder itself is not only valuable in initiating appropriate treatment, but for prognosis as well. In patients with known neuromuscular disorders, preventive measures, such as nocturnal NPPV and cough augmentation, should be offered. Lastly, discussions on long-term ventilation wishes need to occur in all patients with known progressive neurological disorders prior to acute respiratory failure.

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Coma and Brain Death

17

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Abstract

Arousal impairment, as manifested by coma, encephalopathy, and brain death, is a common final pathway for a broad range of diseases, which share the common thread of pathophysiological derangement of the pons, midbrain, thalamus, or simultaneous damage to bilateral thalamocortical projections or bilateral cortices. Coma is a state of complete unresponsiveness to external and internal stimuli, which is typified by the complete failure of normal arousal. Encephalopathy is an impairment of normal arousal in which the level of arousal fluctuates. These manifestations of arousal failure are among the most common derangements in hospitalized patients and patients in the ICU and the etiologies of arousal failure are manifold. In this chapter, the anatomical and physiological bases of arousal failure are discussed. The anatomical and physiological foundations of arousal failure are then used as framework to describe the neurological assessment of comatose or encephalopathic patients and how the neurological assessment leads to neuroanatomical localization of the brain injury leading to arousal failure. The approach to etiological diagnosis and management of patients with coma and encephalopathy are then described based on the principles of neurological localization.

Brain death is defined as the irreversible cessation of clinical brain activity after exclusion of toxic or metabolic confounders. Although the body continues to function for some finite period of time after brain death, somatic death is imminent. In this chapter, the approach to the suspected

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brain-dead patient is described, within the framework of the anatomical and physiological foundations of arousal failure, neurological assessment, and neuroanatomical localization.

Keywords
Coma • Brain death • Encephalopathy • Consciousness • Arousal • Awakening • Emergent assessment • Neurological localization

Introduction

Arousal refers to the process of waking or becoming more vigilant and can occur in response to external or internal stimuli. In contrast, consciousness comprises both arousal and awareness: awareness requires intact cortical function, whereas arousal requires intact subcortical and brainstem function [1]. Immediately after brain injury, a number of disorders of arousal are possible, including death, coma, and encephalopathy [2]. Coma is defined as a state of complete unresponsiveness to external or internal stimuli and is characterized by a failure of arousal and consciousness: patients in coma have no spontaneous eye opening and do not arouse to sensory stimuli [1]. Coma results from severe damage to the brainstem, thalamus, and/or both cerebral hemispheres simultaneously [1]. Encephalopathy is characterized by failure of normal arousal, in which the level of arousal fluctuates [1]. Patients with encephalopathy have an abnormal level of consciousness and arouse inconsistently to internal and sensory stimuli in contrast to patients in coma who arouse to neither internal nor external stimuli [1]. Encephalopathy, like coma, results from damage to the brainstem, thalamus, or both cerebral hemispheres, but the damage is less severe. The neuroanatomical localization of arousal failure to the brainstem, thalamus, or both cerebral hemispheres is the most important principle to consider in the approach to a comatose or encephalopathic patient. Localization of the brain injury producing the arousal failure leads to efficient and timely treatment of the disease.

Brain death is characterized by the irreversible absence of all clinical brain activity after exclusion of toxic or metabolic confounders, such as drug overdose, general anesthesia, or hypothermia [3, 4]. Uniform Determination of Death Act (UDDA) defines death as (1) irreversible cessation of circulatory and respiratory functions and (2) irreversible cessation of all functions of the entire brain, including the brainstem [5]. Therefore, a declaration of brain death is a declaration of death of the patient [5]. Although the body continues to function normally in many clinical situations after brain death, no recovery of neurological function is possible after brain death and progression to somatic death is imminent [3]. Timely recognition and declaration of brain death are paramount to the organ and tissue donation and transplantation effort because the nonneurological organs can continue to function normally for several days after brain death. Nonetheless, timely declaration of brain death is an ethical and practical imperative to avoid impractical expectations by patients' families and futile implementation of health-care resources. In a setting outside of tissue or organ donation, the timely diagnosis of brain death can bring closure to the family. Brain death, as the basis of ultimate futility, is the initiating point for a change in management strategies from active intervention to comfort care with the cessation of life-sustaining therapies.

Epidemiology of Arousal Failure

Coma and encephalopathy are among the most common and most serious disorders affecting patients admitted to intensive care units and gen-

eral medical wards. Despite their epidemiological importance in hospitalized patients, the true impact of disorders of arousal is still not fully recognized. The best approximation of the impact of coma stems from studies of patients with coma due to cardiac arrest. The annual incidence of cardiac arrest alone is in excess of 400,000, and as many as 80% of these patients are expected to be comatose at some point and to have poor neurological outcomes [6, 7]. In a study of critically ill patients who underwent mechanical ventilation, about 15–20% were comatose and arousal failure was frequently implicated as the cause for prolonged mechanical ventilation [8, 9]. In a study of sepsis, 16% of patients were comatose and a low level of consciousness was associated with increased mortality [10, 11]. Furthermore, in patients with critical illness admitted to a respiratory intensive care unit, 30% were comatose [11]. Each of these studies suggests that coma is a serious disease affecting up to one-third of patients admitted to general intensive care units and is probably even more common in patients admitted to neurological ICUs. Importantly, coma is not a serious disease solely because of its high prevalence in hospitalized patients, but the presence of coma is also a powerful predictor of mortality, hospital length of stay, and poor functional outcomes in multiple neurological disorders, including stroke, intracerebral hemorrhage, and traumatic brain injury, and in general medical and surgical intensive care patients [12–15].

Encephalopathy is also common in hospitalized and intensive care unit patients. As many as 30% of patients admitted to medical and surgical hospital wards and 50–90% of patients admitted to an ICU have an encephalopathy [16–18]. Encephalopathy is associated with increased risk of death, prolonged mechanical ventilation, and hospital length of stay [8, 16]. Together, disorders of arousal account for a significant epidemiological problem in hospitalized patients. As the importance of these disorders is increasingly recognized and the mechanisms of arousal are understood, treatment and prevention of arousal failure will continue to evolve.

Anatomy and Physiology of Arousal and Pathogenesis of Arousal Failure

Pathogenesis of Disorders of Arousal

As a general rule, disorders of arousal and consciousness result from significant injury to the upper brainstem, thalamus, thalamocortical projections, or bilateral cortices. The anatomy and physiology of these structures as they pertain to arousal are described below. Figure 17.1 schematically approximates these arousal systems neuroanatomically. Table 17.1 summarizes the components of each of the arousal systems.

Arousal Systems

Arousal or vigilance is mediated by a complex interaction of cortical and subcortical networks. Cortical activation is required for arousal and awareness, but anatomic and physiological data suggest that the cortex does not contain an intrinsic mechanism for the generation and maintenance of arousal [19, 20]. As such, a number of subcortical networks participate in the generation of arousal [21]. These networks include arousal systems located in the brainstem, thalamus, basal forebrain, and hypothalamus. Signals from peripheral sensory organs, such as the eyes, ears, or skin, are detected by sentinel arousal systems within the brainstem, which in turn excite thalamocortical neurons. Sensory transmission within the thalamus also directly excites thalamocortical neurons. Thalamocortical neuron excitation promotes cortical excitation, which is supportive of arousal. The hypothalamus and basal forebrain are also important in arousal, although the precise identification of their role is still under investigation. These systems are summarized in the succeeding sections.

Brainstem Arousal Systems

The brainstem arousal systems comprise the reticular activating system (RAS), the pedunculopontine tegmental and laterodorsal (PPT/LDT)

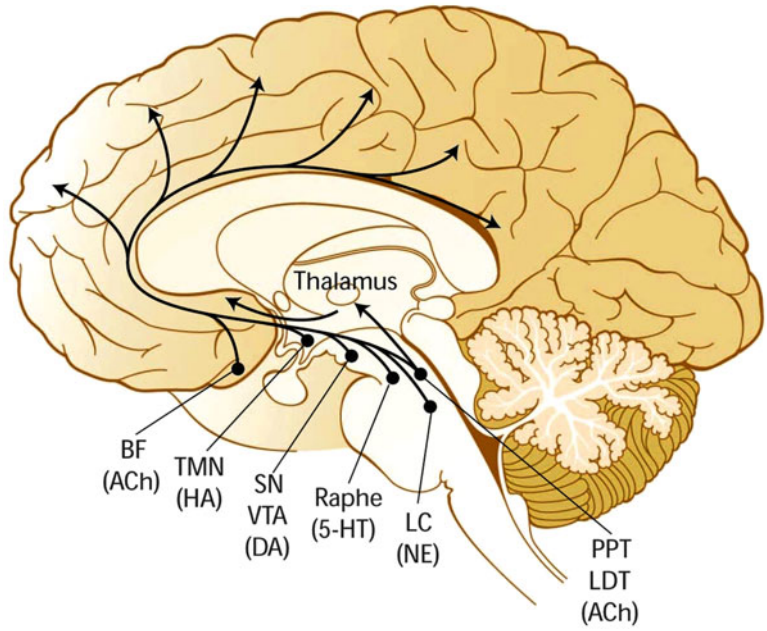

Fig. 17.1 Brain areas important to maintaining arousal. Ascending arousal systems in the brainstem and posterior hypothalamus send projections throughout the forebrain. Cholinergic neurons in the pedunculopontine and laterodorsal tegmental areas (PPT/LDT) activate many forebrain targets, including the thalamus. Adrenergic neurons in the locus coeruleus (LC), serotonergic neurons in the dorsal raphe (DR), histaminergic neurons in the tuberomammillary nucleus (TMN), dopaminergic neurons in the substantia nigra and ventral tegmental area (SN/VTA), and cholinergic neurons in the basal forebrain (BF) excite many cortical and subcortical targets. All of these arousal nuclei are in turn innervated by orexin neurons located in the lateral hypothalamus. Ach, acetylcholine; DA, dopamine; HA, histamine; NE, norepinephrine; 5-HT, serotonin. From Patel SR, White DP, Collop N. "Sleep". In: Crapo JD (ed.) *Bone's Atlas of Pulmonary Medicine, 3rd ed*. Philadelphia: Current Medicine, LLC 2005; 81–93. Reprinted with permission

Table 17.1 Arousal systems

Brainstem arousal systems
Reticular activating system (RAS)
Pedunculopontine tegmental and laterodorsal nuclei (PPT/LDT)
Locus coeruleus (LC)
Substantia nigra pars compacta and ventral tegmental area (SNPC-VTA)
Raphe nucleus (RN)
Thalamic arousal systems
Specific thalamocortical system
Nonspecific thalamocortical system
Basal forebrain arousal systems
Substantia innominata
Nucleus basalis of Meynert
Diagonal band of Broca
Magnocellular preoptic nucleus
Median septum
Globus pallidus
Hypothalamic arousal system
Posterior hypothalamus
Anterior hypothalamus

nuclei, the locus coeruleus, the substantia nigra pars compacta, and the midline raphe nuclei. These nuclei are located in disparate anatomical sites in the brainstem, but each is optimally positioned to broadly send and receive information. Because of their anatomical positioning and broad rostral projections, these nuclei may serve as sentries for the arousal system. The RAS is the best studied of these nuclei and is representative of the structure and function of these systems. The RAS comprises neurons in core nuclei located near the cerebral aqueduct of the midbrain and near the fourth ventricle in the pons [22, 23]. These neurons are interspersed in a weblike reticulum between the ascending and descending fibers, which comprise the motor and sensory tracts as they traverse the brainstem. The RAS neurons have long dendrites that interdigitate those fibers

[23], and are thus optimally situated to integrate information from a wide variety of sources, including sensory input from visual, somatosensory, auditory, and vestibular systems, as well as sensory and motor output from the cerebral cortex, thalamus, and basal ganglia [24, 25]. Ascending arousal signals from the reticular formation to the forebrain are conveyed through two systems: the dorsal system traverses the thalamus and transmits diffusely to the cortex through thalamocortical projections, and the ventral system, which comprises the basal forebrain and hypothalamus, acts as key relay components [26].

Thalamic Arousal Systems

The thalamus is crucial for achieving and maintaining arousal through its connections with the cortex [19, 20]. The thalamus receives and sends data to and from virtually all central nervous system structures. Functionally, thalamic nuclei have been classified into "specific" and "nonspecific" thalamocortical systems through which the thalamus projects to the cortex [27]. "Specific" thalamocortical projections convey information within the sensory, visual, auditory, or motor systems, which have precise neuroanatomical localizations within the cortex and thalamus, and include such thalamic nuclei as the medial and lateral geniculate nuclei and the group of ventral nuclei. In contrast, "nonspecific" thalamocortical projections transmit information from multiple subcortical nuclei, including the reticular nuclei, dorsal raphe, the PPT/LDT nuclei, the locus coeruleus, basal forebrain, and hypothalamus, to multiple cortical regions. Nonspecific thalamocortical projections originate from midline, medial, and intralaminar groups of thalamic nuclei, which are located in the central thalamus. Contrary to initial reports, these central thalamic nuclei actually have a specific neuroanatomical localization, which has drawn into question their identification as "nonspecific" [28]. Because of their connection with the cortex, each of the thalamocortical projection systems can play a role in cortical activation.

Hypothalamic and Basal Forebrain Arousal Systems

The hypothalamus plays a vital role in both arousal and sleep generation. Based on studies in cats, the posterior hypothalamus appears to be the most important hypothalamic center for arousal behaviors, whereas the anterior hypothalamus and hypothalamic–mesencephalic junction promote sleep [29]. Studies of the cellular physiology mediating the influence of the hypothalamus on arousal and vigilance are ongoing. Hypothalamic nuclei comprise many types of neurons, including histaminergic and peptidergic neurons, which produce orexins. Histaminergic neurons are found primarily in the tuberomammillary nucleus and posterior hypothalamus and can influence arousal via projections to the anterior hypothalamus, the dorsal raphe nuclei, the mesopontine tegmentum, the thalamus, the substantia innominata, and directly to the cortex [30]. Histaminergic neurons can influence the firing mode of thalamocortical neurons depending on the relative distribution and activation of distinct histamine receptors (H1R and H2R), which each have different mechanisms of postsynaptic activity [31]. Orexins (hypocretins) are neuropeptides that promote arousal [32]. An orexin deficiency has been hypothesized as a cause of narcolepsy, a disease characterized by hypersomnolence [33–35]. Orexin-producing neurons, located within the posterior and lateral hypothalamic areas in the region of the fornix, are known to have widespread excitatory CNS projections, with densest projections to the locus coeruleus, in addition to other regions of the hypothalamus, the basal forebrain, the thalamocortical system, and to multiple brainstem nuclei [36].

Basal forebrain structures include the substantia innominata, the nucleus basalis of Meynert, the diagonal band of Broca, the magnocellular preoptic nucleus, the medial septum, and the globus pallidus [37]. Neurons in the basal forebrain are a major source of acetylcholine release throughout the brain, and thus play a major excitatory role in cortical activation and arousal [38]. However, unlike thalamocortical

neurons, intact basal forebrain activity is not required for arousal: destruction of the basal forebrain in cats does not abolish cortical activation [39]. The basal forebrain's exact contribution to arousal is still under investigation.

Clinical Assessment and Neurological Examination in Arousal Disorders

Emergent Assessment of a Comatose Patient

The initial assessment of all patients with critical illness should focus on the ABCDs (airway, breathing, circulation, and defibrillation) of Advanced Cardiac Life Support (ACLS) and Advanced Trauma Life Support (ATLS). A full description of ACLS and ATLS guidelines is beyond the scope of this chapter. Relevant materials can be obtained from their respective sponsoring organizations with the American Heart Association for the ACLS and the American College of Surgeons for the ATLS.

After a complete ACLS and/or ATLS survey in a comatose patient, the next step is to perform a rapid neurological assessment to screen for neurological catastrophes which must be intervened upon emergently, such as cerebral herniation. A rapid neurological assessment includes determination of level of consciousness, evaluation for pupil asymmetry and light reactivity, and evaluation of motor function. The most broadly utilized scale to assess level of consciousness is the Glasgow Coma Scale (GCS) [40]. While initially developed for assessment and follow-up of mental status in patients with traumatic brain injury, this 15-point scale is now used extensively in emergency rooms and intensive care units to assess level of consciousness in all patients. To calculate GCS, points are assigned as demonstrated in Table 17.2. The lowest possible GCS score is 3, which corresponds to death, extremely poor prognosis, or deep anesthesia. The highest possible score is 15 and corresponds to a fully awake person. Comatose patients have GCS <9. When patients cannot speak due to an endotracheal tube or tracheostomy, the GCS score is annotated with a "T." Therefore, a patient with endotracheal intubation, no eye opening, and a best motor response of extensor posturing to pain will have a GCS score of 4T. The level of consciousness, including the ability to follow commands, and best motor function are evaluated with calculation of the GCS. While the GCS has been used widely in the evaluation of patients going in and out of a comatose state, a major limitation of the GCS is the noninclusion of cranial nerve assessment as a surrogate of brainstem integrity. The most important cranial nerve to consider is cranial nerve 3. Along with a reduction in the level of consciousness that may be represented by lowering of the GCS, the involvement of the third cranial nerve with pupillary irregularity or dilatation has been used to define the clinical occurrence of transtentorial herniation. In this setting, a reduction in the level of consciousness is the most sensitive sign of herniation, whereas pupillary abnormalities help localize which part of the brain is injured by the herniating brain region [41]. Furthermore, pupils and vital signs should be evaluated for patterns that suggest specific neurological injury. Abnormal pupillary reactivity and respiratory patterns can belie neurological injuries in specific parts of the brain. To address the noninclusion of brainstem evaluation in the GCS, Wijdicks and colleagues

Table 17.2 Glasgow Coma Scale

Eye examination
4 – Eyes open spontaneously
3 – Eyes open to voice
2 – Eyes open to pain
1 – No eye opening
Verbal response
5 – Oriented
4 – Confused
3 – Inappropriate words
2 – Incomprehensible sounds
1 – No verbal response
Motor examination
6 – Obeys commands
5 – Localizing pain stimuli
4 – Withdrawal from painful stimuli
3 – Flexor posturing to painful stimuli
2 – Extensor posturing to painful stimuli
1 – No motor response

developed the *F*ull *O*utline of *UnR*esponsiveness (FOUR) score to assess level of consciousness. Importantly, this score includes a brainstem evaluation and evaluates four components: eye, motor, brainstem, and respiratory pattern [42]. Because of its comprehensiveness in level of consciousness, the FOUR score may eventually replace the GCS in certain clinical situations: the FOUR score can recognize a locked-in syndrome and the different stages of herniation [42]. A full explanation of the pupil evaluation, interpretation of pupil examination findings, and a description of pathological respiratory patterns are included in the "Complete Neurological Assessment" section that follows this section. Concurrent presence of hypertension, bradycardia, and hyperventilation comprises the "Cushing's reflex," which is seen frequently in patients with intracranial hypertension. This triad is a physiological response that can maintain cerebral perfusion in the setting of high intracranial pressure through systemic hypertension, increased cardiac filling time, and decreased cerebral blood volume (through hyperventilation-induced arteriolar vasoconstriction) [43]. If the rapid neurological assessment suggests cerebral herniation, impending herniation, or intracranial hypertension, then medications to reduce intracranial pressure should be emergently initiated ("Brain Code," see "Emergent Therapies for Arousal Failure" section below).

After the initial ACLS and ATLS surveys and rapid neurological assessment, providers should continue to use the ABCs as a guide to emergent evaluation in patients with critical neurological illness. There are a number of special considerations in patients with emergently critical neurological illness, which warrant a specialized "neurological ABC survey." First, comatose patients (GCS <9) lose the ability to "protect the airway." This means that these patients lack normal upper airway muscular tone because of their neurological injury. On examination, comatose or encephalopathic patients are often snoring loudly or "gurgling" because of the poor upper airway muscular tone. Therefore, spontaneous ventilation is more difficult because of high upper airway resistance, and the risk of aspiration is increased. In general, comatose patients (GCS <9) undergo endotracheal intubation for airway protection ("A" in the neurological ABC survey) to facilitate ventilation and minimize the risk of aspiration and pulmonary complications. Because of inadequate ventilation and possible aspiration in the setting of critical neurological injury, patients may develop hypercapnia and hypoxia which can seriously exacerbate neurological injuries, especially those with mass effect (see "Emergent Therapies for Arousal Failure" section). Therefore, acutely comatose patients should be adequately ventilated or hyperventilated using the combination of bag mask ventilation with adequate FiO_2 to maintain normal oxygenation and an oral or nasopharyngeal airway to maintain airway patency until endotracheal intubation can be achieved. During bag mask ventilation and after endotracheal intubation, initial goals of normocapnia ($PaCO_2$ 35–39 mmHg) and normal oxygenation (SaO_2 95–100% or PaO_2 >80 mmHg) should be set (breathing, "B" in the neurological ABC survey). After identification of the neurological insult, these goals may be modified.

Patients with critical neurological illness can present with a wide range of cardiac rhythms and blood pressures (circulation, "C" in neurological ABC survey). Again, standard ACLS guidelines take immediate precedence in the emergent assessment of a comatose patient. Therefore, unstable cardiac rhythms and very low blood pressures (SBP <80 mmHg) should be assessed using the ACLS guidelines. At this stage in the emergent assessment, the precise etiology of the neurological injury may still not be known, although the history and examination may point to a likely cause. In the comatose patient who does not require ACLS resuscitation, blood pressure should be initially evaluated with consideration of all possible etiologies of critical neurological illness. Thus, blood pressure goals are normally set to a fairly broad range until the etiology of the neurological injury is identified (usually in parallel to establishing adequate ventilation). At this stage in the assessment, suggested blood pressure goals are systolic blood pressure <200 mmHg and mean arterial pressure >70 mmHg [44]. By employing an initially broad

Table 17.3 Emergent assessment of the comatose patient

1. *ACLS or ATLS primary and secondary surveys*
2. *Rapid neurological assessment* Glasgow Coma Scale calculation Pupillary examination
3. *Neuro ABC survey* *A*irway—endotracheal intubation for patients with GCS <9 *B*reathing—bag mask ventilation to achieve normocapnia and normal oxygenation *C*irculation—achieve SBP <200 mmHg and MAP >70 mmHg Head *C*T when stabilized

blood pressure goal range, the practitioner seeks a balance between treating the neurological injury and avoiding iatrogenic exacerbation of the injury. For example, patients with acute ischemic stroke may require higher blood pressures to maintain perfusion of ischemic brain territories, whereas patients with intracerebral or subarachnoid hemorrhages will ultimately require lower blood pressures (<160 mmHg) to prevent worsening of the hemorrhage [45, 46]. This practice has been borne out in the authors' personal experience and studied to some degree in traumatic brain injury [44]. This goal blood pressure range also helps guide the use of anesthetic agents during endotracheal intubation, which may result in precipitous swings in blood pressure. The goal of blood pressure management at this stage is stabilization to allow for safe transport of the patient to obtain a computed tomography study of the brain (head *C*T, another "C" in the neurological ABC survey). In conjunction with the history and examination, the head CT will hopefully lead to early definitive diagnosis and possible treatment of the etiology of the neurological injury. Table 17.3 summarizes the emergent assessment of the comatose patient.

Importantly, while this section focuses primarily on the emergent assessment of an acutely comatose patient, use of the assessment outlined in Table 17.3 is an efficient strategy to initiate the evaluation of *any patient* with critical neurological illness, even if their condition does not appear to be changing acutely or if they appear to be clinically stable. Using this strategy, the clinician has a reliable framework to ensure that catastrophic processes are recognized and treated early.

Complete Neurological Assessment of the Comatose Patient

The purpose of a complete neurological examination in comatose patients is to localize the lesion responsible for failure of arousal. This more comprehensive evaluation should be performed after emergent assessment and stabilization of an acutely comatose patient. Neurological examination and anatomical localization allow for an accurate assessment of the condition of the patient as an important guide for immediate and future investigation and therapy. The neurological examination in the comatose patient is performed with the same format as in conscious patients, except that the approach is modified for performance in a patient who cannot cooperate or follow commands. The standard format of the general neurological examination proceeds through each of the following neurological systems: mental status and/or level of consciousness; cranial nerves; motor system; sensory system; reflexes; coordination; and gait. In a poorly arousable patient, assessment of the level of consciousness is paramount and takes precedence over the standard mental status examination, in which the content of consciousness is assessed. In fact, further assessment of the content of consciousness (e.g., language, calculation, memory) is not possible or reliable without an adequate level of arousal. Cranial nerves, motor and sensory systems, and reflexes are also examined in detail. Examination of coordination and gait is more difficult in an uncooperative patient and does not usually contribute to neuroanatomical localization in disorders of arousal.

In disorders of arousal, accurate assessment of the level of consciousness is imperative. The approach to examination of a patient's level of consciousness is to ascertain the degree of wakefulness, orientation, and attention. The first step in examining an unresponsive patient (after the rapid neurological assessment) is to observe

the patient for a period of time to assess whether the patient arouses spontaneously (to internal stimuli). The next step is to assess the patient's responsiveness to external (examiner-induced) stimuli. These stimuli should be applied in a graded fashion from least to most noxious. Common stimuli include the following: voice or loud sound, especially calling of the patient's name; painful stimulus (pinch or rub) applied to arm, leg, trapezius muscle, chest, or orbit; nasopharyngeal stimulation with a cotton swab; and in-line suctioning of endotracheal or tracheostomy tube. Attention should be paid to the amount of stimulation needed for arousal, the level of arousal achieved with stimulation, and how long the patient remains aroused after discontinuation of the stimulus. If the patient arouses reliably, then the level of attention and orientation can be assessed by performing a limited mental status exam or a Folstein Mini-Mental Status Exam (MMSE). The patient should be asked to follow commands or verbalize if not intubated. If verbal, the patient should be asked to state his name, the location, the date or year, season, and reason for hospitalization. Cues can be given, but the use of cues should be accounted for when assessing level of arousal, i.e., reliance on cues suggests less orientation and more abnormal arousal. Patients should also be asked to follow commands. Midline commands (e.g., eye opening and closing, sticking out the tongue) should be tested first, followed by appendicular commands (e.g., showing two fingers or thumbs up). An ability to follow appendicular commands belies more complex processing and higher level of arousal than obeying midline commands alone. A patient in coma will not follow commands, open eyes, arouse to any painful or noxious stimuli, or respond in any meaningful way. An encephalopathic patient will arouse, open eyes, and follow commands inconsistently.

The cranial nerve examination is important for localization of the lesion responsible for the altered level of consciousness and to monitor for disease progression. The RAS, which controls cortical activation and arousal, traverses the brainstem longitudinally and is anatomically proximate to many cranial nerves and their nuclei, especially those from the midpons and more rostrally. Examination of the cranial nerves proceeds in the numerical order of the nerves, with exclusion of the olfactory nerve (cranial nerve 1). The function of the optic nerve (cranial nerve 2) can be examined through several approaches. In an unresponsive patient, the integrity of optic nerve function is examined by testing for pupillary function, blink reflex to a threat stimulus, and the ability to track visual stimuli. When testing pupils, light from the examiner is directed onto the retina and pupil constriction (miosis) is triggered. Miosis requires an intact optic nerve, midbrain, oculomotor nerve (cranial nerve 3), and parasympathetic nervous system. Furthermore, in normal patients, when light is directed into one eye, both pupils constrict consensually. Pupillary constriction and the consensual response in the contralateral eye are dependent on the Edinger–Westphal nucleus, which is located in the midbrain. To activate this pathway, an examiner's light stimulates retinal ganglion cells located in the retina. Most of the retinal ganglion cells project via the optic nerves and tracts to the lateral geniculate nucleus and ultimately the visual cortex to encode visual information. However, a number of neurons project to the pretectal nucleus of the midbrain and thus form the afferent limb of the pupillary light reflex. From the pretectal nucleus, the pathway projects to the Edinger–Westphal nucleus, which gives rise to the pupil-constricting fibers of the oculomotor nerve. A lesion along these pathways could cause an inability of one or both pupils to constrict, depending on the precise location of the lesion and the structures affected. A lesion involving the optic nerve will lead to an inability of both pupils to constrict consensually to light directed into the affected eye because the afferent limb of the pupillary light reflex is dysfunctional. This type of lesion can be highlighted using the swinging flashlight test, where the examiner's light is directed into each eye alternately. During this test, when the light is directed into the affected eye, both pupils dilate. In contrast, when the light is directed into the normal eye, both pupils constrict appropriately. Lesions affecting the optic nerve in isolation rarely affect the level of

consciousness. The most common location for lesions affecting both the pupillary light reflex and the level of consciousness is in or near the midbrain and such lesions usually result in oculomotor nerve or nucleus dysfunction [47]. Examination of oculomotor nerve function will be discussed below.

A test for reflexive blink to visual threat is another way to test the optic nerve in an unresponsive patient. The examiner can move his fingers or hand toward the patient's eye in a brisk, "threatening" manner and can even present the stimulus within quadrants of confrontational visual field testing. Reflexive blink to a visual threat requires an intact optic nerve, which serves as the afferent limb of the reflex pathway, and an intact facial nerve, which serves as the efferent limb of the pathway producing a blink response [47]. However, an absent reflexive blink to visual threat is nonlocalizing because lesions producing a failure to blink to threat have been postulated in multiple disparate locations, including the striate cortex, higher-order visual processing centers, frontal eye fields, and mid- to upper brainstem [48]. Reflexive visual stimulus tracking can also be examined in an unresponsive patient. Like the blink-to-threat pathway, tracking of visual stimuli is also controlled through a complex neurological pathway. Nonetheless, the afferent limb is also the optic nerve. To test for the ability to track visual stimuli, various items and objects can be moved through the visual fields. Most directly, the patient can be asked to follow fingers or a face with his eyes. Several powerful stimuli to test the ability to track are the human face, paper money, and photographs of loved ones. Another tracking stimulus is the optokinetic nystagmus (OKN) strip or wheel, in which a strip of paper or wheel with alternating colors is moved across the patient's visual fields. OKN strips or wheels trigger nystagmus in normal patients. In order to have a normal response to OKN testing, patients must have intact optic nerves in addition to intact higher-order cerebral processing centers, such as in the occipital and parietal cortices [49]. OKN testing can be used to test for normal optic nerve and visual function in an unresponsive patient, but absent OKN is difficult to localize [47].

The oculomotor nerve (cranial nerve 3) has two principal functions (1) control of pupillary constrictors and (2) extraocular eye movements. Again, bilateral symmetrical pupillary constriction requires intact optic nerves (cranial nerve 2), midbrain, oculomotor nerves (cranial nerve 3), and parasympathetic nervous system function [47]. The efferent limb of the pupillary light reflex begins at the Edinger–Westphal nucleus, which gives rise to parasympathetic fibers that travel within the medial aspect of the midbrain before joining onto the surface of the oculomotor nerve. The nuclei of the oculomotor nerve also are located in the medial aspect of the midbrain and give rise to the fibers that control eye movements. The eye movements controlled by the oculomotor nerve include all of the cardinal directions (upward, downward, medially) in the ipsilateral eye, except lateral and the combination of downward and medial. The lateral and downward/medial movements are controlled by the lateral rectus nerve (cranial nerve 6) and trochlear nerve (cranial nerve 4), respectively.

Integrity of the oculomotor nerve and its nuclei is tested by testing pupillary function and eye movements. In the case of the oculomotor nerve, derangement of the parasympathetic fibers causes marked pupillary dilation ("blown pupil"). Damage to Edinger–Westphal and oculomotor nuclei within the midbrain causes bilateral failure of pupillary constriction and pupils that are midsized (2–4 mm) and unreactive. In contrast, damage to the pons can lead to pupils that are pinpoint and poorly reactive, due to interruption of descending sympathetic pathways and consequently unopposed parasympathetic activity produced by the midbrain [47]. Because of the close proximity of the oculomotor nerve and nuclei to the cerebral aqueduct and the RAS, lesions affecting pupil reaction often are accompanied by arousal failure. Pupil size and reactivity, in addition to other exam findings, can help identify the precise neuroanatomical location of the responsible lesion. For example, bilaterally midsized pupils and loss of consciousness would be attributable to a medial midbrain lesion. In contrast, a fixed and dilated pupil without alteration in consciousness would likely be attributable

to ipsilateral oculomotor nerve compression without impingement on the midbrain. A fixed and dilated pupil with an alteration in consciousness suggests oculomotor nerve dysfunction in or near the midbrain. Small, unreactive ("pinpoint") pupils bilaterally and arousal failure are attributable to a lesion in the upper pons.

In the unresponsive patient, extraocular movements are observed for the oculomotor and abducens nerves (cranial nerves 3 and 6, respectively). Trochlear nerve (cranial nerve 4) function is difficult to test in unconscious patients. In the unresponsive patient, spontaneous eye movements and passive eye positioning should first be observed to determine any obvious weakness. Weakness with gaze in any direction might be observed in the patient's spontaneous eye movements. The patient can be asked to track a visual stimulus or a powerful tracking stimulus, which can be moved across the patient's visual fields. Examples of powerful tracking stimuli include a human face, high denomination paper money, or an OKN strip or drum. In an unresponsive or uncooperative patient, eye movements can be tested using the oculocephalic reflex, also sometimes referred to as testing for doll's eyes. For this test, the examiner moves the patient's head laterally from side to side and observes the patient's lateral eye movements. Normally, tonic activity bilaterally within the vestibular systems drives the eyes to the contralateral side. This activity is balanced unless the head is moved. When the head is moved laterally, activity increases in the vestibular system ipsilateral to the direction of head movement and decreases in the vestibular system contralateral to the head movement. *Thus, in a patient with normal eye movements, the eyes move in the opposite direction to the head turn*. This test can also be performed using vertical head movements. A normal oculocephalic reflex requires a normal vestibular apparatus, vestibulocochlear nerve (afferent limb, cranial nerve 8), brainstem, oculomotor nerve (efferent limb, medial eye movement), and abducens nerve (efferent limb, lateral eye movement) [47]. An absence of eye movements with oculocephalic testing can be due to diffusely abnormal brainstem activity or no brain activity at all. However, this test should be interpreted with caution because conscious patients can suppress the oculocephalic reflex with gaze fixation on a distant object. If the oculocephalic reflex is present in some directions but not others, then the test should be interpreted to determine which particular extraocular muscles are weak and ultimately which nerves or their nuclei have failed: the oculomotor nerves control medial eye movements and the abducens nerves control lateral eye movements.

If the oculocephalic reflex is absent, then a stronger test to confirm absent eye movements is the vestibuloocular reflex or cold caloric test. For this test, water that has been cooled for 5 min with ice is instilled continuously into one external auditory meatus for 2 min. The eyes are observed for movement during and several minutes after the infusion. After several minutes to allow rewarming, cold water should be infused into the contralateral ear. Like the oculocephalic reflex, a normal cold caloric response requires a normal vestibular apparatus, vestibulocochlear nerve (afferent limb, cranial nerve 8), brainstem, oculomotor nerve (efferent limb, medial eye movement), and abducens nerve (efferent limb, lateral eye movement). As mentioned, normally tonic activity bilaterally within the vestibular system drives the eyes to the contralateral side. Cooling of the tympanic membrane disrupts this balance. *Thus, in a patient with normal pons and midbrain activity, inhibition of tonic activity by tympanic membrane cooling causes the eyes to move toward the cooled ear*. The lateral and medial eye movements are mediated by the abducens and oculomotor nerves, respectively. If the patient also has intact cortical activity, a corrective saccade away from the cooled ear will also be present. The classic mnemonic "COWS: *c*old *o*pposite, *w*arm *s*ame" refers to the corrective saccade produced by the different water temperatures used in caloric testing. This mnemonic has little clinical utility in the comatose patient because cortical activity is usually absent or markedly abnormal. In patients where the cold caloric response is asymmetrical or absent on one side, the other clinical and neurological examination data should be interpreted to determine the location of the lesion. In a patient with

absent pons and midbrain activity, the eyes will remain in the midline during cold caloric testing on both sides. Eye motion abnormalities often accompany loss of consciousness because of the close proximity of extraocular movement nuclei to the RAS, especially in the midbrain.

Brain injury that produces arousal failure can often produce certain patterns of eye movements, which can aid in localization [47]. Ocular bobbing is produced by pontine lesions and is defined by a rapid downbeat and slow upward phase [47]. Midbrain lesions can produce retraction nystagmus, conversion nystagmus, and sunsetting eyes with forced downgaze [47]. Ping pong eyes and periodic alternating gaze are induced by injuries to both hemispheres, cerebellar vermis, or the midbrain [47]. Though rare, when present with coma or encephalopathy, these eye movement abnormalities can portend neurological catastrophe.

In the unresponsive patient, the corneal reflex is the most reliable way to test trigeminal nerve (cranial nerve 5) function. In this test, the cornea is stimulated, which causes a blink reflex in both eyes. This reflex requires a normal ipsilateral trigeminal nerve, pons, and bilateral facial nerves. Like the pupillary light response, there is a consensual blink response to corneal stimulation. A component of the corneal reflex is also controlled by the contralateral parietal lobe [48]. The trigeminal nerve is the afferent limb of this reflex and can be stimulated using techniques of graded intensity. The most benign form of stimulation is to gently touch or move the patient's eyelashes. If the patient blinks symmetrically, then the corneal reflex is intact and no further corneal stimulation is needed. Corneal stimulation techniques of greater intensity include placing drops of normal saline in the eye and touching a tapered cotton swab to the cornea. The cotton swab provides the highest level of corneal stimulation. Care should be taken with repeated corneal reflex testing to avoid the region directly in the front of the lens because a corneal abrasion in this location could affect vision. It is advisable to test the corneal reflex as distal from the lens as possible, such as where the sclera and the cornea intersect.

The facial nerve (cranial nerve 7) can be tested by observing passive face posture, such as palpebral fissure width and the nasolabial fold. As mentioned above, the efferent limbs of the blink and corneal reflexes are controlled by the facial nerve. Facial weakness should be interpreted in conjunction with other clinical variables as it relates to an altered level of consciousness. The vestibulocochlear nerve (cranial nerve 8) is tested as described above, using the oculocephalic and vestibuloocular reflexes. The glossopharyngeal and vagus nerves (cranial nerves 9 and 10, respectively) are tested via gag and cough. Patients with a severely diminished level of consciousness often have weaker or more poorly coordinated gag and cough. The exact etiology of this poor coordination is not clear as the glossopharyngeal and vagal nuclei are often spared by lesions that affect the level of consciousness. Comatose patients are usually intubated for airway protection because even with a present gag and cough, there is a high risk of poor ventilation, aspiration, and pneumonia. The spinal accessory nerve and hypoglossal nerves are not commonly tested in the unresponsive patient.

The brainstem is responsible for control of the pattern of breathing. Lesions within the brainstem can cause pathologic breathing patterns that are typified by the location of the lesion. Cheyne–Stokes breathing is defined by short periods of hyperpnea followed by short periods of apnea and may be associated with other signs of heightened arousal, such as improved motor exam or eye opening. Cheyne–Stokes breathing usual results from bilateral thalamic injury, injury to widespread bilateral cortical projections, or metabolic derangements, and is therefore frequently associated with arousal failure. Apneustic breathing is associated with pontine injury and is characterized by long inspiratory pauses. Central neurogenic hyperventilation is characterized by sustained hyperventilation with respiratory rates >40 breaths per minute. This pattern localizes injuries to both cerebral hemispheres, the pons, or the midbrain. Cluster breathing is defined by irregular clusters of breaths, followed by pauses of irregular duration. Injuries to both hemispheres, the pons, or rostral medulla can result in cluster breathing. Ataxic breathing results from medullary lesions, is defined by a completely

irregular pattern (the "atrial fibrillation" of respiratory patterns), and can signal impending respiratory failure.

As in the examination of the cranial nerves, the motor system is examined first by passive observation. The examiner should note whether the patient is moving symmetrically, briskly, spontaneously, and whether the patient is posturing any extremities. Next the examiner should ask the patient to follow commands in the midline and with all four of his extremities. If the patient is conscious, confrontational power testing can be performed as in the classic neurological examination. Similarly, if the patient is awake and lucid, the sensory system can be tested in detail. However, in the unresponsive patient, the motor and sensory systems are tested together as the patient responds to painful stimuli delivered centrally and peripherally. When a painful stimulus is applied, if the patient moves any extremities or grimaces, then there is evidence that a sensory signal is being processed. If the patient moves his extremity in a complex way in response to a painful stimulus, especially against gravity, then the patient has localized. Localization is not stereotyped: the patient may perform a different or very purposeful action with each painful stimulus, which belies higher cortical processing. In contrast, withdrawal of the extremity to a painful stimulus can be stereotyped and is often within the plane of gravity. Posturing of the extremities or absent extremity movement portends severe neurologic injury. There are two types of posturing: extensor (decerebrate) and flexor (decorticate) posturing. Extensor posturing is associated with poorer clinical outcomes and usually results from injuries to larger brain territories, including the pons and midbrain. With extensor posturing, painful stimuli trigger a very stereotyped response in which the patient extends and pronates one or both arms to his side, extends both wrists, extends both legs, and plantar flexes the feet. In contrast, with flexor posturing, painful stimuli also trigger a stereotyped response except that the arms flex at the wrist and elbow. Flexor posturing is also associated with poor neurological outcomes, but is caused by injury to less brain territory than extensor posturing, usually involving the regions rostral to the upper midbrain. Because of the uncertainly regarding the precise localization of these posturing reflexes, it is advised to use the terms extensor and flexor instead of decerebrate or decorticate posturing. To determine with certainty whether the patient's movement is a withdrawal or posture, the patient's hand should be placed on his abdomen and a painful stimulus applied to the upper arm. With localization or withdrawal, the patient will move the arm away from the painful stimulus. With a posture, the arm will move in a stereotyped manner irrespective of the stimulus location. Applying a painful stimulus to the lower extremities may also trigger a triple flexion response, in which the hip and knee flex and the ankle dorsiflexes. This finding is a spinal cord reflex and is consistent with severe neurological dysfunction. While flexor and extensor posturing are associated with poor neurological outcomes, both require brain activity. The triple flexion reflex may persist in the absence of brain activity and in the setting of brain death.

Tendon reflexes play a diminished role in the examination of the comatose patient, as compared to the traditional neurological examination. The jaw jerk reflex is a reflex that tests the integrity of the trigeminal nerve and its nuclei. Elevated jaw jerk reflexes can be seen with lesions above the trigeminal nuclei and with diffuse metabolic and toxic processes that can cause altered level of consciousness. Other tendon reflexes can be tested for hyper- or hyporeactivity, which can be seen in the setting of toxic and metabolic derangements, or asymmetry which could help localize the neurological injury in conjunction with other clinical data and the neurological examination as described in the preceding sections.

Clinical Determination of Brain Death

Brain death (death by neurological criteria) is characterized by the irreversible absence of all clinical brain activity (determined on neurological examination as described in the preceding

paragraphs). Criteria for brain death can only be met if an inciting central nervous system injury is identified, all possible metabolic and toxic causes are excluded, and the patient is normothermic and not hypotensive [3, 50]. For brain death determination, a thorough neurological examination reveals none of the following: response to painful stimuli, including extensor or flexor posturing (although spinal cord reflexes presenting as preserved tendon reflexes, extensor plantar responses, triple flexion in the lower extremities are permitted); blink to threat or corneal stimulation; response to nasopharyngeal stimulation; pupillary response; eye movement on cold caloric testing bilaterally; gag or cough; and effort to breathe above the set ventilator rate [3, 50]. After confirming the absence of brain activity through neurological examination, an apnea test is performed, based on the premise that the drive to breathe is one of the strongest stimuli of brainstem function (especially of the medulla). For this test, the patient is removed from the ventilator and examined for breathing efforts. Blood gases are measured during this test: a rise in $PaCO_2$ to greater than 60 mmHg or a rise in $PaCO_2$ to >20 mmHg above baseline without an effort to breathe is consistent with absent brain activity. The criteria for determination of brain death are summarized in Table 17.4.

Table 17.4 Determination of brain death (modified from Wijdicks et al. 2010)

1. Prerequisites
a. Establish irreversible cause of coma
b. Achieve normal core temperature (>36°C)
c. Achieve normal systolic blood pressure (>100 mmHg)
d. Perform at least one neurologic examination, depending on local statutes
2. Neurologic assessment
a. Coma (complete unresponsiveness)
b. Absent pupillary response
c. Absent ocular movements, including with cold caloric testing
d. Absent corneal reflex
e. Absent facial muscle movement
f. Absent gag and cough reflexes
g. No evidence of breathing effort on apnea testing
3. Ancillary tests
a. Employed if neurologic assessment cannot be completely performed or is inconclusive
b. No evidence of cerebral blood flow on either:
– Nuclear scan
– Cerebral angiography
c. No evidence of electrical activity on electroencephalogram
4. Documentation
a. Time of brain death is the time when $PaCO_2$ exceeds 60 mmHg or >20 mmHg above baseline
b. Time of death is the time of interpretation when an ancillary test is employed
c. An organ procurement organization must be notified

Occasionally, patients become hemodynamically unstable during apnea testing, and/or items of the neurological examination cannot be completed. Under these circumstances, ancillary testing can be used to infer the absence of brain activity. Foremost amongst these tests are conventional cerebral angiogram and cerebral blood flow testing using a radioactive tracer (nuclear medicine). The absence of cerebral blood flow on these tests, in conjunction with no evidence of clinical brain activity, is consistent with brain death. Other tests that support the diagnosis of brain death include an electrosilent electroencephalogram and transcranial dopplers or CT angiogram without evidence of blood flow. However, these tests are less reliable. Ancillary testing is not required for declaration of brain death if the clinical examination, including the apnea test, is confirmatory.

Importantly, the diagnosis of brain death is the equivalent of death, and this fact should be stressed when counseling families [5]. The time of death is designated as the moment that the $PaCO_2$ rises to greater than 60 mmHg or >20 mmHg above the patient's baseline $PaCO_2$, without an effort to breathe [3]. The definitions and determination of somatic death and brain death vary slightly depending on state, local, and hospital statutes. Brain death determination should be in accordance with these statutes. The American Academy of Neurology seeks to standardize brain death determination by publishing an evidence-based guideline [3, 50].

Etiology and Differential Diagnosis of Arousal Failure

The etiologies of coma and encephalopathy are broad. However, the common theme, as described in the preceding sections, is that the etiology of arousal failure must affect the upper brainstem (especially in the region of the cerebral aqueduct or fourth ventricle), thalamus, or thalamocortical projections or bilateral cortices simultaneously. To determine the etiology of coma, the clinician must take into account the patient's past history, the time course of the insult, associated symptoms and signs, the localization of the injury based on the neurological examination as described above, clinical imaging such as CT or MRI scans, and pertinent laboratory results. A helpful mnemonic for considering all possible etiologies in neurological disorders, especially for neurological disorders such as coma with a myriad of potential etiologies, is "VITAMINS C/D," which stands for *v*ascular, *i*nfection, *t*rauma, *a*utoimmune/inflammatory, *m*etabolic, *m*edications, *m*igraine, *i*ntracranial pressure (high or low), *n*eoplasms, *s*eizures, *c*erebrospinal fluid disorders (hydrocephalus), and *d*evelopmental/congenital anomalies. Vascular injuries, such as focal cerebral ischemia due to ischemic stroke, global cerebral ischemia due to cardiac arrest, intracerebral hemorrhage, or subarachnoid hemorrhage, can cause disorders of arousal by directing damaging the brainstem or thalamus. Also, mass effect caused by cerebral edema after vascular injuries can lead to elevated intracranial pressure, obstructive hydrocephalus, and herniation, which can in turn damage the arousal system through direct compression. Vascular injuries tend to occur abruptly, and in the case of ischemic stroke and intracerebral hemorrhage, are likely to present with neurological dysfunction localizable to brainstem or thalamic injury when they also affect the level of consciousness.

Infections, such as meningitis or abscess, can affect the level of consciousness through at least two mechanisms. The infectious process and associated inflammatory process can impair cortical activity diffusely through changes in blood flow, altered CSF dynamics, and cerebral edema. Alternatively, the infection itself may directly involve or impinge upon the arousal system. Infections can present acutely, subacutely, or chronically, may be associated with fever and leukocytosis, and usually cause an abnormal cerebrospinal fluid. Trauma frequently causes failure of arousal either by direct traumatic injury to the arousal system or through compression of the arousal system due to concomitant cerebral edema. Trauma is usually suggested by the history and presentation and evidence of trauma on physical examination. Autoimmune or inflammatory etiologies can cause failure of arousal through mechanisms similar to infection. The clinical presentation may be identical to infection, except that there is no evidence of an infectious etiology and other serum markers of inflammation are elevated, such as ESR, ANA, or ANCA.

Metabolic derangements and medications are among the most common causes of arousal failure and can be diagnosed by history or laboratory testing [51]. Common metabolic derangements that can alter consciousness are hypo- and hyperglycemia, hypo- or hypernatremia, hyperuremia, hypercarbia, hypoxia, hyperammonemia, and hypercalcemia. Common medications implicated in failure of arousal include ethanol, benzodiazepines, narcotics, barbiturates, antiepileptics, muscle relaxants, antihistamines, and withdrawal from or overdose of medications [8, 51]. The elderly and patients with preexisting brain injuries are particularly sensitive to both metabolic derangements and medications which alter the level of consciousness [51]. Migraine is an unusual cause of arousal failure. However, basilar migraine is a rare subtype of migraine that can affect the level of consciousness, which might be suspected based on a history of headaches and is usually a diagnosis made after exclusion of other more sinister diagnoses, such as basilar artery stroke.

High intracranial pressure is often heralded by arousal failure and is most frequently caused by vascular lesions, infections, neoplasms, and hydrocephalus. High intracranial pressure can cause arousal failure through at least two mechanisms

(1) cerebral herniation, where the pressure due to a lesion in a neighboring brain region forces brain tissue into the arousal system, and (2) diffusely elevated pressure causing diffuse cortical dysfunction. Neoplasms can cause arousal failure if they grow directly into the arousal system, by compression of the arousal system after growth from a nearby focus, or through derangement of the arousal system by vasogenic edema. Seizures cause arousal failure through several mechanisms (1) status epilepticus (convulsive or nonconvulsive) is associated with poor arousal; (2) during a single seizure or cluster of seizures, patients may be poorly arousable, depending on the size of the seizure focus; and (3) patients may fail to arouse reliably during the postictal period and after administration of sedating antiepileptic medications. Seizure as a cause of arousal failure is suggested by a history of epilepsy, witnessed clonic activity or other seizure-related signs, such as tongue biting, and by an electroencephalogram with evidence of ongoing or recent seizure. Hydrocephalus can compress and cause dysfunction in the thalamus and midbrain and can also lead to diffuse dysfunction of bilateral cortical projections. Hydrocephalus can be congenital or develop as a sequela of neoplasm, CNS infection, inflammatory disease, hemorrhage, or ischemic stroke. In patients with congenital hydrocephalus, failure of a shunt device should also be considered a possible cause of arousal failure.

The differential diagnosis of arousal failure most commonly includes coma and encephalopathy. However, other less common states of arousal failure must be considered. These states include brain death (as discussed above), a vegetative state, minimally conscious state, locked-in syndrome, akinetic mutism, and psychogenic coma. A vegetative state is one of the possible outcomes of coma, especially if the coma results from extensive bilateral cortical, subcortical white matter, or thalamic injuries with relative sparing of the brainstem. In the vegetative state, the brainstem arousal systems are preserved; therefore, patients in a vegetative state may present with periodic episodes of spontaneous arousal, arouse reflexively to external stimuli, and have spontaneous eye opening, but all other components of consciousness and cognition are absent [52]. In a vegetative state, arousal occurs in the absence of consciousness because awareness is deficient from extensive cortical or subcortical white matter injury. The reflexive behaviors of the vegetative state are in contrast to the complete unresponsiveness of coma. In fact, the vegetative state may represent a transitional state from the unarousable unresponsiveness of a coma to a partially responsive state. By convention, a vegetative state persisting for longer than 1 month is referred to as a "persistent" vegetative state, whereas the persistence of a vegetative state for more than 3 months following nontraumatic brain injury is called a "permanent" vegetative state, in light of the low likelihood of recovery of independent function [52]. In the minimally conscious state, responses to both environmental and internal stimuli can be present, but this state differs from the vegetative state in that intermittent, inconsistent behavioral evidence of consciousness is discernible, which suggests awareness [53]. For example, a patient in the minimally conscious state may sporadically, but unreliably, follow commands, attend to or track a human face or voice, or make meaningful speech [54]. As in a vegetative state, patients in a minimally conscious state have extensive cortical or subcortical white matter injury, but the injury is thought to be less severe, allowing for greater awareness [52]. The significance of distinguishing the minimally conscious state from a vegetative state lies in the likelihood of recovery. While significant recovery from a permanent vegetative state is highly unlikely, measurable recovery from the minimally conscious state is increasingly recognized as possible [55, 56]. In fact, therapies aimed to improve arousal and awareness, such as deep brain stimulation (see Treatments for Arousal Failure section), are under investigation in minimally conscious state patients.

The locked-in syndrome clinically appears to be a failure of arousal, but is actually a state of complete deefferentation due to severe injury to the ventral pons. Locked-in patients have normal arousal and awareness because the RAS (located in the dorsal pons) is spared. Classically,

locked-in patients can only communicate with the examiner through blinking and/or upward gaze. In a comatose patient with brainstem injury, it is important to ask the patient to look up and blink in the initial assessment to ensure that the locked-in syndrome is not missed. Patients with brainstem ischemic stroke, especially due to basilar occlusion, brainstem hemorrhage, or demyelination can become locked-in. Also, patients undergoing pharmacological paralysis with neuromuscular blocking agents or with severe acute demyelinating inflammatory polyneuropathy may present similarly. In patients with locked-in syndrome, an electroencephalogram showing normal cortical activation is a helpful diagnostic adjunct.

Akinetic mutism is another rare form of arousal failure characterized by an abulic, emotionless, frequently motionless state, but with intact visual tracking [54]. Painful stimuli trigger variable responses, including no response or extensor posturing. Reflexive blinking and grimacing to pain remain intact and frontal release signs may be present. Akinetic mutism results most commonly from lesions to bilateral anterior cingulate gyri due to hemorrhage or ischemia which leads to an inability to initiate movements. Akinetic mutism can also result from thalamic or basal ganglia injuries [54].

Treatments of Arousal Failure

Emergent Treatments in Arousal Failure

Emergent therapies for patients with arousal failure focus on data gathered during the emergent assessment of the comatose patient (see Emergent Assessment of the Comatose Patient section). As discussed, the initial assessment of all critically ill patients begins with the primary and secondary ACLS surveys. The specific therapies recommended in the ACLS algorithms are beyond the scope of this chapter. In the rapid neurological assessment and the neurological ABC survey, important clinical data are gathered specific to treatment of critically ill patients with neurological injury with the aim of predicting whether the acutely comatose patient is stable for further diagnostic assessment (head CT, MRI, complete neurological examination). As discussed above, comatose patients (GCS <9) usually undergo endotracheal intubation for airway protection and receive bag mask ventilation with an oral or nasal airway to achieve normocapnia and normal oxygen saturation until the etiology of the neurological injury is known.

Blood pressure is treated during the neurological ABC survey with goal blood pressures of systolic blood pressure <200 mmHg and mean arterial pressure >70 mmHg. Commonly used medications to decrease blood pressure include labetalol (10–20 mg intravenously every 10 min as needed) and hydralazine (10 mg intravenously every 10 min as needed). Labetalol should be avoided in patients with bradycardia. Nicardipine can be administered to lower blood pressure as a continuous intravenous drip, in principle providing more precise minute-to-minute control of blood pressure. Use of nitrates and sodium nitroprusside to lower blood pressure should be avoided for emergent use in comatose patients with possible or confirmed intracranial hypertension because these agents can increase intracranial pressure by causing profound venodilation [57]. Neosynephrine, dopamine, and norepinephrine are commonly used medications to increase blood pressure. Neosynephrine and dopamine have the advantage that they can be administered temporarily through a peripheral intravenous line. Norepinephrine, while more effective at increasing blood pressure, requires central venous access. Neosynephrine should be avoided in patients with bradycardia because it can cause reflexive bradycardia.

A rapid neurological assessment will determine whether the patient has a neurological injury that requires immediate intervention. If the patient exhibits clinical evidence of intracranial hypertension (e.g., coma, pupillary abnormalities, Cushing's triad), a "brain code" should be performed (summarized in Table 17.5). A "brain code" is the systematic administration of therapies to lower intracranial pressure. First, the head of the patient's bed should be elevated

Table 17.5 "Brain Code"—emergent therapies for intracranial hypertension

1.	*Physical interventions—optimize cerebral venous drainage* Move head of bed to >30° Secure head in the midline to avoid jugular vein compression Ensure that no compressive bandages or tape are on the neck Obtain central venous access in the femoral vein
2.	*Hyperventilation—decreases cerebral blood volume through cerebral arteriolar vasoconstriction* Goal $PaCO_2$ 28–32 mmHg Use bag mask ventilation until patient is endotracheally intubated
3.	*Mannitol (1–2 g/kg)—decreases cerebral volume by promoting water movement into blood vessels from brain tissue* Can be administered through a peripheral or central IV
4.	*Hypertonic saline (2–23.4%)—decreases cerebral volume by promoting water movement into blood vessels from brain tissue*
5.	*Intracranial pressure monitoring device* External ventricular drain, intraparenchymal monitor, subarachnoid bolt Will require head CT prior to placement

>30° and the tape used to secure the endotracheal tube should be confirmed not to be compressing the jugular veins. Second, the patient should be hyperventilated, with the goal $PaCO_2$ of 28–32 mmHg. Hyperventilation can be achieved by increasing respiratory rate or tidal volume in a patient undergoing mechanical ventilation or through bag mask ventilation (goal rate 25–30 breaths per minute) in a patient prior to imminent endotracheal intubation. An end-tidal CO_2 monitor should be employed where possible to guide hyperventilation therapy because prophylactic and chronic hyperventilation can lead to worsening brain injury and must therefore be avoided. Third, mannitol (20% or 25%, 1–2 g/kg) should be administered through either a central or peripheral intravenous line. Mannitol creates an osmotic gradient allowing water to flow out of both the edematous and normal brain, which decreases cerebral volume, and consequently, intracranial pressure. Fourth, hypertonic sodium chloride (2–23.4% NaCl) should be administered, through a peripheral (≤2% NaCl) or central (>2% NaCl) intravenous line. Fifth, a device to measure intracranial pressure (ICP) and guide subsequent therapy should be placed. These devices can include an external ventricular drain (EVD) if the ventricles are not compressed, an intraparenchymal monitor, or a subarachnoid bolt. Prior to placement of an ICP monitor, efficacy of intracranial hypertension therapy can be monitored clinically by noting changes in level of consciousness, pupillary reactivity, and abnormal vital signs. In patients with intracranial hypertension, a goal cerebral perfusion pressure (CPP) of greater than 60 mmHg should be met to avoid concomitant cerebral ischemia. The CPP is defined as the difference between the mean arterial pressure (MAP) and ICP. In a patient with an ICP monitor, MAP should be supported to maintain CPP >60 mmHg. In a patient with no ICP monitor and presumed intracranial hypertension, the clinician should assume an ICP ≥ 20 mmHg; therefore, the MAP should be maintained to ≥80 mmHg.

Importantly, while the mortality of acute intracranial hypertension is high, with frequent progression to brain death, there is significant potential for good neurological outcomes. In a prospective study of 28 patients with acute intracranial hypertension and cerebral herniation, 16 (~60%) patients died, including the 13 patients who progressed to brain death. However, with aggressive medical therapy as described in the preceding paragraphs, seven (25%) of these patients were functionally independent in approximately 1 year [41]. In a retrospective study of the efficacy of 23.4% NaCl in the reversal of cerebral herniation, 5 of 68 patients (7.4%) had mild or moderate disability at discharge [58]. Both of these studies indicate that despite the high risk of severe disability and death due to intracranial hypertension and cerebral edema, prompt recognition and initiation of a "brain code" can lead to good neurological outcomes in up to 25% of affected patients.

During the "brain code," a clinician should place a central intravenous line, if not already completed in the ACLS or preceding steps in the neurological ABC survey. Hypertonic saline solutions >2% require central administration, as

does norepinephrine. Mannitol remains an option to treat intracranial hypertension before central intravenous access is attained because mannitol can be given through a peripheral intravenous line. Furthermore, critically ill patients commonly require central venous access for administration of multiple medications and frequent blood testing. If intracranial hypertension is suspected, then internal jugular and subclavian lines should be avoided until control of intracranial pressure is achieved. Compression of the internal jugular vein can worsen intracranial hypertension by decreasing venous outflow. Both subclavian and jugular venous line placement require positioning of the patient in the Trendelenberg position, which can worsen intracranial hypertension by decreasing venous outflow. Therefore, when emergently treating comatose patients, especially those with possible intracranial hypertension, a femoral venous line should be placed with the patient in reverse Trendelenberg position. Because of the risk of infection, consideration of placing an intravenous line at another site within 48 h is strongly advised.

Acute Treatments for Arousal Failure

The most important principle in the treatment of arousal failure is to remove the etiological agent if possible. In the cases of a brain neoplasm, hydrocephalus, infection, autoimmune disease, seizure, medications, and metabolic derangements, removal or successful treatment of the etiology may be possible and likely if identified early. In contrast, in neurological injury that leads to permanent damage to the arousal systems, such as global cerebral ischemia due to cardiac arrest, focal cerebral ischemia due to stroke, or traumatic brain injury, treatment is focused on minimizing brain injury and optimizing recovery.

A number of disease-specific acute interventions are available to treat the cause of arousal failure or to prevent further damage. Acute ischemic stroke is treated with intravenous tissue plasminogen activator (TPA) if the patient presents within 3 h of stroke onset and antiplatelet therapy if no TPA is given. Intractable intracranial hypertension can be treated with craniectomy. Intracerebral and subarachnoid hemorrhages require lowering of blood pressure to systolic blood pressure <160 mmHg, correction of any coagulopathy, and emergent surgery or endovascular treatment if indicated. Subdural hemorrhages in comatose patients require evacuation and correction of any coagulopathy. Central nervous system infections require prompt broad-spectrum antimicrobial treatment and corticosteroids, if indicated. Status epilepticus and recurring seizures require urgent antiepileptic drug treatment.

Neuroprotection is an active field of clinical and translational neuroscience research. The hypothesis underscoring studies of neuroprotection is that certain therapies, such as pharmacological agents, can reduce ischemia-induced neuronal death. Numerous pharmacological agents have been studied extensively in the laboratory and in clinical trials. Unfortunately, no drug has proven to be reliably neuroprotective in clinical trials, despite the apparent neuroprotective success of many pharmacologic agents in animal studies. However, recent research has generated considerable hope for better chances of recovery from coma following global cerebral ischemia, such as that due to cardiac arrest. Therapeutic hypothermia (32–34°C) applied to comatose survivors of cardiac arrest was shown to significantly improve neurological outcomes in approximately one of every six patients [59, 60]. This neuroprotective intervention has provided the most substantial improvement in neurological outcomes after cardiac arrest since the advent of modern cardiopulmonary resuscitation. Because of the neuroprotective efficacy of therapeutic hypothermia, in a 2005 advisory statement, the American Heart Association recommended “cooling unconscious survivors after out-of-hospital cardiac arrest to 32–34°C for 12–24 h when the initial rhythm is ventricular fibrillation” [61]. This advisory statement adds that therapeutic hypothermia may also be beneficial for other cardiac arrhythmias or inhospital cardiac arrest [61].

Treatments for Chronic Arousal Failure

Translational neuroscience and clinical trials of pharmacological agents and other therapies to maximize recovery of ischemic brain and optimize utility of noninjured brain are also ongoing. One exciting topic of considerable interest has developed around the possibility of deep brain stimulation for patients with disorders of consciousness. A recent case report in which stimulation of central thalamic nuclei was reported to improve arousal in a patient with a minimally conscious state after traumatic brain injury lends proof of concept to this possibility [62]. This technology might also be expanded to comatose survivors of global cerebral ischemia due to cardiac arrest. In fact, several case reports and case series have been published over the last decade that detail use of deep brain stimulators in these patients [63–67]. The largest series comes from Japan, reporting 10-year follow-up data from 26 patients with deep brain stimulators implanted in either the central thalamic nuclei or the mesencephalic reticular nuclei [64]. Although many patients remained in a vegetative state after stimulation, meaningful behaviors and interaction with the external environment were observed in several patients after several months of stimulation. Although deep brain stimulation remains experimental in survivors of cardiac arrest with impairment of arousal, there is strong biological plausibility supporting recruitment of cortical arousal patterns by stimulation of deeper nuclei in the thalamus and brainstem.

Several pharmacological agents to aid in restoration of arousal have also been studied in the laboratory and in selected small patient populations. The most promising of these agents is modafinil (Provigil) because of its low side-effect profile. Modafinil appears to have a number of pharmacophysiologic effects, including sharpening thalamocortical coupling and increasing extracellular norepinephrine levels within the brainstem [68]. Both of these effects promote arousal. Modafinil has been reported to promote increased wakefulness in narcoleptics and shift workers and in patients with obstructive sleep apnea, multiple sclerosis, and stroke with consequently impaired arousal. Studies of patients in coma have not been extensively reported. The most severe side effect of modafinil is that it inhibits some cytochrome p450 enzymes and may affect the levels of other medications. Modafinil can also cause headache, nervousness, and hypertension [69]. Methylphenidate (Ritalin) has been studied in patients with coma, especially those with traumatic brain injury [70]. Like modafinil, methylphenidate increases extracellular concentrations of norepinephrine and therefore promotes arousal. Studies of methylphenidate in traumatic brain-injured patients suggested that administration of methylphenidate leads to decreased hospital and ICU lengths of stay [70]. There is a theoretical risk of cardiac side effects in patients treated with methylphenidate. Additionally, zolpidem (Ambien), a common hypnotic used as a sleep aid in healthy patients, has been shown to have a paradoxical effect in some patients with disorders of consciousness. Specifically, administration of zolpidem to patients with arousal failure can increase arousal through an undetermined mechanism [71].

Conclusion

Arousal failure, as manifested by coma and encephalopathy, is a common final pathway for a broad range of diseases, which share the common thread of pathophysiological derangement of the pons, midbrain, thalamus, or simultaneous damage to bilateral thalamocortical projections or bilateral cortices. Though frequently devastating, early recognition and treatment of these diseases can lead to good neurological outcomes. Expeditious therapy requires a careful, pragmatic assessment of the patient using a solid understanding of the neuroanatomical localization of arousal failure. As we continue to explore the anatomy and physiology of arousal systems and the pathophysiology of arousal failure in the laboratory and at the bedside, established therapies to promote arousal will be optimized and new therapies will emerge.

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Neurotoxicology Emergencies

18

Laura M. Tormoehlen

Abstract

Exposure to pharmaceutical, occupational, or environmental toxins may cause or increase the risk of certain neurological emergencies. Early identification of the exposure and the toxin can be instrumental in the diagnosis and management of toxin-induced neurological emergencies. This chapter reviews the toxins associated with hyperthermic syndromes, ischemic and hemorrhagic stroke, seizures and status epilepticus, weakness, and acute encephalopathy.

Keywords

Amphetamine • Cocaine • Malignant hyperthermia • Neuroleptic malignant syndrome • Serotonin syndrome • Status epilepticus

Toxin-Induced Hyperthermic Syndromes

General Considerations

Regulation of body temperature is a balance between the production and dissipation of heat. Toxin-induced hyperthermia occurs when heat production is increased or the body's ability to dissipate heat is impaired [1]. The complex process of thermoregulation is regulated by hypothalamic control of the sympathetic nervous system and by mitochondrial oxidative phosphorylation. Serotonin and sympathomimetic syndromes cause hyperthermia via heat generation from increased motor activity and uncoupling of oxidative phosphorylation as well as impaired dissipation from vasoconstriction of cutaneous blood vessels [1]. Anticholinergic syndrome causes hyperthermia by muscarinic inhibition, resulting in impaired sweating in the setting of severe agitation and hyperactivity. Severe salicylate toxicity results in hyperthermia via uncoupling of oxidative phosphorylation. Withdrawal of gamma-aminobutyric acid (GABA) agonists, including ethanol, benzodiazepines, barbiturates, baclofen, and gamma-hydroxybutyrate (GHB), can cause hyperthermia via autonomic overstimulation.

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Serotonin Syndrome

Introduction

The serotonin syndrome was first defined by Sternbach in 1991 [2], although the clinical manifestations of the syndrome were described in patients taking monoamine oxidase inhibitors (MAOIs) and tryptophan in 1960 [3]. It is typically characterized by mental status changes, autonomic instability, and motor hyperactivity. The practitioner must have a high level of suspicion for this diagnosis, as the altered mental status often precludes a reliable history and many patients present without one or more of the cardinal findings [2]. In addition, symptoms of mild or early serotonin syndrome such as diarrhea, tremor, and irritability may be overlooked, and thus the causative medications may not be discontinued. The severe complications of serotonin syndrome include seizures, rhabdomyolysis, respiratory failure, and cardiac arrhythmia.

Epidemiology

Serotonin syndrome occurs most often when two or more proserotonergic medications are used in combination [2, 4]. It is difficult to determine the true incidence of this syndrome, as the majority of cases remain unrecognized [5]. Symptoms of moderate-to-severe toxicity occur in 17% of patients who overdose on selective serotonin reuptake inhibitors (SSRIs), and death occurs in 0.2% [6]. In a survey of consecutive admissions to an inpatient toxicology unit, serotonin syndrome occurred in 14% of patients with overdose of a single SSRI [7]. In patients taking nefazodone, the incidence of two or more symptoms of serotonin syndrome is 0.4 cases per 1,000 treatment-months [5]. A large number of pharmaceuticals have been reported in association with serotonin syndrome. The major drug categories implicated are SSRIs, MAOIs, tricyclic antidepressants (TCAs), antibiotics, opioid analgesics, antiemetics, migraine abortives, drugs of abuse, and herbal supplements (Table 18.1).

Pathophysiology

Serotonin, or 5-hydroxytryptamine (5-HT), is synthesized by hydroxylation and decarboxylation of L-tryptophan. After vesicular release from neurons, serotonin is removed from the synapse by the serotonin reuptake transporter. The first step in serotonin metabolism is deamination, preferentially performed by monoamine oxidase type A, to 5-hydroxyindoleacetic acid (5-HIAA). There are seven subgroups of serotonin receptors, and serotonin syndrome is likely a combination of effects at several of these individual receptor types. However, activity of 5-HT_{2A} receptors appears to be integral to the development of serotonin syndrome [8–12].

Serotonin syndrome is characterized by hyperactivity of both central and peripheral serotonergic neurons. In the central nervous system, serotonergic neurons are located mainly in the midline raphe nuclei of the brainstem [13]. These structures are involved in thermoregulation, wakefulness, muscle tone, and chemoreceptor-mediated emesis. Serotonergic receptors are abundant in the peripheral nervous system, and are responsible for gastrointestinal motility and vascular smooth muscle tone [14]. The function of serotonergic neurons in the central and peripheral nervous systems correlates directly with the clinical features of serotonin syndrome: cognitive dysfunction, autonomic instability (hyperthermia, hypertension, diarrhea), and motor hyperactivity.

The possible mechanisms of increased serotonergic activity are (1) increased serotonin synthesis, (2) increased serotonin release, (3) direct serotonin receptor agonism, (4) inhibition of serotonin reuptake, and (5) decreased serotonin metabolism. There are xenobiotics that may cause serotonin syndrome by each of these mechanisms. Tryptophan supplementation results in increased serotonin synthesis. Amphetamines and cocaine cause increased serotonin release. Sumatriptan, buspirone, and lysergic acid diethylamide are all serotonin receptor agonists. The SSRIs and TCAs inhibit serotonin reuptake, and the MAOIs decrease serotonin metabolism. Serotonin syndrome is caused by an acute increase in intrasynaptic serotonin, and is a drug reaction for which all patients are at risk [15].

Clinical Features/Diagnosis

The original diagnostic criteria proposed by Sternbach [2] require the addition or titration of a serotonergic agent, without a recent addition or

Table 18.1 Serotonergic xenobiotics

Category	Drugs	Mechanism
Selective serotonin reuptake inhibitors	Citalopram Fluoxetine Fluvoxamine Paroxetine Sertraline	Serotonin reuptake inhibitors
Tricyclic antidepressants	Amitriptyline Clomipramine Desipramine Doxepin Imipramine Nortriptyline	Serotonin reuptake inhibitors
Monoamine oxidase inhibitors	Isocarboxazid Moclobemide Phenelzine Selegiline Tranylcypromine	Decreased serotonin metabolism
Other antidepressants/ anxiolytics	Buspirone	Serotonin receptor agonist
	Trazodone Venlafaxine	Serotonin reuptake inhibitors
Analgesics	Meperidine Pentazocine Tramadol	Serotonin reuptake inhibitors
Antimigraine medications	Sumatriptan Other triptans	Serotonin receptor agonists
Antimicrobials	Linezolid	MAO inhibitor
	Ritonavir	Cytochrome 3A4 inhibitor
Supplements and over-the-counter drugs	Dextromethorphan	Serotonin reuptake inhibitor
	L-tryptophan	Increased serotonin synthesis
Drugs of abuse	Amphetamines Cocaine MDMA	Increased serotonin release
	LSD	Serotonin receptor agonist
Miscellaneous	Fenfluramine Reserpine	Increased serotonin release
	Bromocriptine L-dopa Lithium	Nonspecific increase in serotonin activity

MDMA 3,4-methylenedioxymethamphetamine, *LSD* lysergic acid diethylamide.

titration of a neuroleptic, and three of the following clinical findings: altered mental status, agitation, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, diarrhea, incoordination, and fever. Other possible etiologies, including infection and withdrawal, must be excluded.

In 2003, the Hunter Serotonin Toxicity Criteria were published in a comparison study to the Sternbach criteria in a retrospective analysis of prospectively collected data. The Hunter criteria allow the diagnosis of serotonin syndrome with the administration of a serotonergic agent within the past 5 weeks and any one of the following scenarios: (1) spontaneous clonus, (2) inducible clonus and agitation or diaphoresis, (3) ocular clonus and agitation or diaphoresis, (4) tremor and hyperreflexia, and (5) muscle rigidity and hyperthermia (>38°C) and either ocular or inducible clonus. The Hunter criteria were more sensitive (84% vs. 75%) and slightly more specific (97% vs. 96%) than the Sternbach criteria [16].Symptoms of motor hyperactivity, manifested by spontaneous, inducible, or ocular clonus, are the hallmark of serotonin toxicity [2, 3, 15, 17, 18]. Mydriasis occurs in more than 30% and tachycardia in 40% of patients with serotonin syndrome [16].

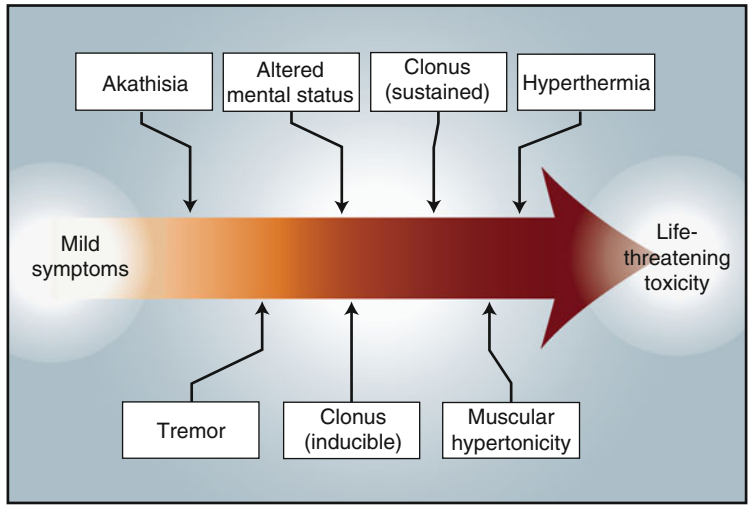

Fig. 18.1 Spectrum of clinical features of serotonin syndrome(Used with permission. Boyer and Shannon [4]. Copyright © 2005. Massachusetts Medical Society. All rights reserved)

Serotonin syndrome represents a spectrum of symptoms (Fig. 18.1) and usually develops and progresses over a few hours. Individual patients with serotonin toxicity might not meet the Hunter or Sternbach criteria for diagnosis. This is most likely to occur early in the course prior to the onset of more severe symptoms [19], or late in the course when muscle rigidity has become severe enough to prevent tremor or clonus [16]. Patients with life-threatening serotonin toxicity are more likely to have muscle rigidity and hyperthermia, and may require intubation if the rigidity causes respiratory compromise [16].

Differential Diagnosis

Neuroleptic malignant syndrome, malignant hyperthermia, sympathomimetic syndrome, anticholinergic syndrome, strychnine toxicity, tetanus, and salicylate toxicity are alternate toxicologic diagnoses to consider. Meningoencephalitis, stiff-person syndrome, nonconvulsive status epilepticus, hyperthyroidism, and sepsis also bear consideration in the differential diagnosis.

The symptom onset and progression of neuroleptic malignant syndrome is slower, occurring over days to weeks instead of hours. In addition, neuroleptic malignant syndrome is a hypokinetic syndrome characterized by bradykinesia and rigidity, whereas mild or moderate serotonin syndrome is a hyperkinetic syndrome. The rigidity of severe serotonin syndrome is usually much more prominent in the lower extremities than in the upper extremities [20].

Serotonin syndrome, neuroleptic malignant syndrome, and malignant hyperthermia are all hyperthermic syndromes, but the causative medications are vastly different. A comprehensive history regarding recent changes in medications will typically favor one diagnosis over another. Because of the medications involved in malignant hyperthermia, this syndrome is very unlikely to occur outside of the operating room. There is, unfortunately, no laboratory test that will accurately distinguish between serotonin syndrome and neuroleptic malignant syndrome. There may be differences in the levels of neurotransmitter metabolites in cerebrospinal fluid [21, 22]; however, the results of these specialty labs may not be available in time to be clinically helpful.

Anticholinergic and sympathomimetic syndromes are both associated with agitation, mydriasis, tachycardia, hypertension, and tremor. In contrast to serotonin syndrome, anticholinergic syndrome is characterized by absent bowel sounds, dry skin, and normal reflexes. Those with sympathomimetic syndrome will exhibit excessive neuromuscular activity that can be difficult

to differentiate from the tremor and clonus of serotonin syndrome. The key to the diagnosis rests in the history, although a reliable history is not always available. Fortunately, the mainstay of treatment for all of these syndromes is cooling, benzodiazepines for agitation and increased muscle activity, intravenous fluids, and supportive care.

Treatment

The first steps in management of serotonin syndrome are removal of the causative agents and provision of supportive care. Many cases of serotonin syndrome will resolve within 24 h of treatment initiation. In patients with mild symptoms (tremor and agitation without fever or autonomic instability), intravenous fluids and benzodiazepines may be adequate. However, any clinical deterioration should prompt a rapid, aggressive response [15, 16].

The etiology of hyperthermia in serotonin syndrome is severe, excessive muscle activity; thus, antipyretics may not be effective in its management. Benzodiazepines are useful in decreasing muscle activity and attenuating the hyperadrenergic response [15], but benzodiazepines and external cooling alone may not be effective in treating the rigidity and hyperthermia of severe serotonin syndrome. Paralysis with nondepolarizing agents, immediately followed by orotracheal intubation and mechanical ventilation, should be considered for patients with hyperthermia (temperature >38.5°C), severe truncal rigidity, or a rising pCO_2 [4, 15, 16].

Cyproheptadine, an antihistamine with nonselective antiserotonergic effects, may be considered in patients with moderate or severe symptoms. It has been shown to prevent serotonin syndrome in animal models [23, 24]. Human case series detail improvement in symptoms after administration of cyproheptadine [15, 25–27]. The recommended dosing of cyproheptadine is an initial dose of 12 mg, followed by 2 mg every 2 h until symptoms improve. Maintenance dosing is 8 mg every 6 h [4]. Cyproheptadine is available in pill form only, but it may be crushed and administered via a nasogastric tube. Resolution of mydriasis after cyproheptadine administration has been reported [26]. While this finding has not been validated as a diagnostic tool, it may support the diagnosis of serotonin toxicity.

Chlorpromazine is a phenothiazine antipsychotic that has antiserotonergic properties. It has also been reported as an effective symptomatic therapy for serotonin syndrome. This medication is not routinely recommended because serotonin syndrome is often difficult to distinguish from neuroleptic malignant syndrome, and chlorpromazine may worsen neuroleptic malignant syndrome. It may also cause hypotension, as well as increasing the risk of seizures and dystonic reactions [20]. However, if the diagnosis is certain and a parenteral treatment is desired, chlorpromazine 50–100 mg may be given intramuscularly [4].

Serotonin syndrome can be life-threatening and is underrecognized. A high level of clinical suspicion will lead to accurate diagnosis, and appropriate treatment can prevent significant morbidity and mortality.

Neuroleptic Malignant Syndrome

Introduction

Neuroleptic malignant syndrome is an idiosyncratic drug reaction to dopamine antagonists that was first reported in 1960 [28]. It is characterized by hyperthermia, diffuse rigidity, autonomic instability, and encephalopathy. Many patients who are prescribed neuroleptics are also prescribed antidepressants, so neuroleptic malignant syndrome and serotonin syndrome must be considered simultaneously. The severe, life-threatening complications of neuroleptic malignant syndrome include rhabdomyolysis, acute renal failure, and respiratory failure. Appropriate, prompt consideration of medication effect as a cause of encephalopathy and hyperthermia is critical to avoid these potential complications.

Epidemiology

The reported incidence of neuroleptic malignant syndrome with therapeutic use of neuroleptics ranges from 0.02 to 2.4% [29–34]. It is most

common with typical neuroleptics, but has been reported with the atypical neuroleptics and antiemetics as well [30, 35]. The mortality rate is around 10% [29, 31]. Risk factors for development of neuroleptic malignant syndrome with therapeutic doses of neuroleptics are young age [31], use of the depot formulation of fluphenazine [33], intramuscular administration [36], presence of mental retardation [37], higher dose of neuroleptic [37], psychomotor agitation [37–39], and dehydration [39]. In a retrospective review of the California Poison Center database, the incidence of neuroleptic malignant syndrome in acute overdose was 1.2% for typical neuroleptics and 0.3% for atypical neuroleptics [40].

Pathophysiology

The exact pathophysiology of neuroleptic malignant syndrome is not yet clear; however, dopamine blockade likely plays a central role in the generation of neuroleptic malignant syndrome. Of the drugs known to cause neuroleptic malignant syndrome, dopamine blockade is the common mechanism of action. The cerebrospinal fluid of patients with neuroleptic malignant syndrome has lower concentration of the dopamine metabolite homovanilic acid than controls [41]. In addition, withdrawal of dopaminergic medications can produce a syndrome similar to neuroleptic malignant syndrome [42, 43], and dopaminergic drugs are useful in the treatment of neuroleptic malignant syndrome. Elevation of catecholamines in the plasma and urine [44], as well as the cerebrospinal fluid [41], suggests that the autonomic dysfunction of neuroleptic malignant syndrome is related to sympathoadrenal hyperactivity [45].

Clinical Features/Diagnosis

The diagnosis of neuroleptic malignant syndrome should be entertained for hyperthermia or rigidity in the setting of neuroleptic therapy or recent withdrawal of dopaminergic medications. Levenson's criteria allow for diagnosis of neuroleptic malignant syndrome in the presence of all three major criteria: fever, rigidity, and elevated serum creatine phosphokinase (CPK). If only two of the major criteria are present, the diagnosis may be made in the presence of four of the minor criteria: tachycardia, abnormal blood pressure, tachypnea, altered consciousness, diaphoresis, and leukocytosis [46].

The onset of neuroleptic malignant syndrome is usually insidious and occurs over days, although acute onset within hours of neuroleptic administration does occur [47]. Nearly all cases of neuroleptic malignant syndrome occur within 1 month of neuroleptic initiation. With supportive care and discontinuation of the offending agent, average recovery time is 7–10 days [47]. A rating scale has been proposed for following the clinical course of neuroleptic malignant syndrome [48]. It is based upon severity of hyperthermia, extrapyramidal symptoms, autonomic instability, altered consciousness, leukocytosis, and CPK elevation. This rating scale may be used to objectively determine severity over time.

Differential Diagnosis

Because neuroleptic malignant syndrome is an idiosyncratic adverse drug reaction, it remains a diagnosis of exclusion. Some laboratory findings (leukocytosis and elevation of CPK) can be supportive; however, no single laboratory abnormality can secure the diagnosis. Therefore, a complete diagnostic evaluation should be performed, including electrolyte panel with calcium and magnesium, renal and hepatic function tests, creatine kinase level, complete blood count, urinalysis, lumbar puncture, and neuroimaging of the brain [49].

The differential diagnosis for neuroleptic malignant syndrome is similar to that of serotonin syndrome and includes malignant hyperthermia, central nervous system infection, anticholinergic delirium, nonconvulsive status epilepticus, salicylate poisoning, baclofen withdrawal, thyrotoxicosis, and heat stroke [49, 50].

Treatment

Stabilization of vital signs and removal of the offending agent(s) are the primary steps in management of neuroleptic malignant syndrome. Severe hyperthermia has been associated with poorer outcome [51], so prompt institution of cooling measures is indicated. Aggressive volume resuscitation and repletion of electrolytes are important, as dehydration is a common presenting feature of neuroleptic malignant syndrome

[49, 50]. Complications of neuroleptic malignant syndrome include aspiration pneumonia, respiratory failure, rhabdomyolysis with subsequent renal failure, and coagulopathy [44, 50]. Patients should be carefully monitored for these complications in an intensive care setting.

Supportive care measures may be sufficient treatment in milder cases of neuroleptic malignant syndrome; however, in more severe cases, pharmacological treatment may be indicated. Although the efficacy of benzodiazepines is modest [52], they are indicated as first-line therapy for agitation and may be effective in treating mild neuroleptic malignant syndrome. A parenteral dose of lorazepam at 1–2 mg is a reasonable initial treatment [50].

Dantrolene is a peripheral muscle relaxant that attenuates calcium release at the sarcoplasmic reticulum of skeletal muscle via inhibition of the ryanodine receptor [53]. Neuroleptic malignant syndrome-related hyperthermia is partially due to the heat produced by muscular rigidity. This tonic, diffuse contraction may also cause rhabdomyolysis. Dantrolene should be considered in patients with severe rigidity and hyperthermia. An initial dose of intravenous dantrolene 1–2.5 mg/kg of body weight should be administered, followed by 1 mg/kg every 6 h. Tapering or transition to oral dantrolene may be made after 48–72 h, although symptoms may return if this change is made prematurely [50, 53]. Dantrolene has been associated with drug-induced hepatitis, so hepatic function should be monitored during treatment [49, 50]. Dopamine agonists and benzodiazepines may be given in combination with dantrolene, but dantrolene should not be given with calcium channel antagonists because of risk of cardiovascular collapse [50].

In addition to the heat produced by rigidity, the hyperthermia of neuroleptic malignant syndrome may also be related to dopamine blockade in the anterior hypothalamus, resulting in inhibition of heat-loss pathways [53]. Dopamine agonists have been associated with reduced time to recovery [54] and mortality rates [55]. First-line dopamine agonist therapy is bromocriptine 2.5 mg orally 2–3 times daily or oral amantadine 200–400 mg/day in divided doses [50]. Both of these medications may be given by nasogastric tube if necessary. Bromocriptine may worsen underlying psychosis and may cause hypotension. If a parenteral agent is necessary, L-dopa can be given intravenously at 50–100 mg/day in divided doses [56]. L-Dopa [57], bromocriptine [58], and amantadine [59] have all been reported to increase central serotonergic activity, so they should be avoided if serotonin syndrome remains in the differential diagnosis.

Severe neuroleptic malignant syndrome that is refractory to dantrolene and dopamine agonists may respond to electroconvulsive therapy (ECT) [60, 61]. ECT may also be effective for the underlying condition for which the neuroleptic was prescribed. It is a reasonable treatment choice for neuroleptic malignant syndrome if idiopathic malignant catatonia is a possible alternative diagnosis [50].

Acute withdrawal of dopamine replacement therapy may cause a neuroleptic malignant-like syndrome. Symptom onset usually occurs 3–4 days after discontinuation of dopaminergic medications, and is usually characterized by worsening of baseline rigidity followed by hyperthermia and altered consciousness [42]. Treatment of neuroleptic malignant-like syndrome is discontinuation of any medications with dopamine blocking activity, and reinstitution of L-dopa therapy [42, 43].

Malignant Hyperthermia

Introduction

Malignant hyperthermia is a rare, autosomal dominant pharmacogenetic disorder of calcium regulation in striated muscle that was first described in the 1960s [62]. It manifests as a hypermetabolic response to inhaled volatile anesthetics and the depolarizing muscle relaxant succinylcholine. Increased carbon dioxide (CO_2) production, hyperthermia, tachycardia, tachypnea, muscle rigidity, and rhabdomyolysis are the classic characteristics of malignant hyperthermia. Complications of malignant hyperthermia include hyperkalemia-induced arrhythmias, compartment syndrome, congestive heart failure, bowel ischemia, disseminated intravascular coagulation, rhabdomyolysis-induced renal failure, and death. Prompt recognition of the early signs of malignant

hyperthermia, which are an increase in end-tidal carbon dioxide, tachycardia, and rigidity, is critical [63].

Epidemiology

Estimates of malignant hyperthermia susceptibility range from 1 in 200 to 1 in 250,000 [64, 65], depending upon geographical location and prevalence of malignant hyperthermia susceptibility genes. In the state of New York, the prevalence rate of malignant hyperthermia is 1 in 100,000 surgeries [66]. The risk for developing malignant hyperthermia is higher in males than in females [63, 66]. A successful anesthesia with agents known to trigger malignant hyperthermia does not exclude the possibility of malignant hyperthermia during future anesthesias [63].

Pathophysiology

The clinical effects of malignant hyperthermia are secondary to uncontrolled calcium release from the sarcoplasmic reticulum, resulting in sustained muscle contraction [67]. Anaerobic metabolism is increased, resulting in hypoxia and acidosis. This is followed by rhabdomyolysis, which may produce hyperkalemia and acute renal failure. Uncoupling of oxidative phosphorylation produces heat, manifested as hyperthermia.

Malignant hyperthermia is associated with abnormalities in both the ryanodine (RYR1) and dihydropyridine (DHP) calcium channels, and is inherited as an autosomal dominant disease [67, 68]. Most people with a genetic susceptibility to malignant hyperthermia do not exhibit signs of myopathy; however, there are a few genetic myopathies that are linked to malignant hyperthermia. These include central core and multiminicore myopathies, as well as King-Denborough syndrome and Brody myopathy [68, 69]. While not true malignant hyperthermia, inhalational anesthetics and succinylcholine may produce severe hyperkalemia and rhabdomyolysis in patients with Duchenne and Becker muscular dystrophies [68].

Clinical Features/Diagnosis

The initial sign of malignant hyperthermia is an unexplained rise in end-tidal CO_2 during a general anesthetic procedure that involves a triggering agent [67]. This is followed by tachycardia, hypertension, generalized muscle rigidity or masseter spasm, metabolic acidosis, and hyperthermia. Given the causative agents associated with malignant hyperthermia, the diagnosis will nearly always be made in the operating room or post-anesthesia recovery room. Those patients with symptoms consistent with malignant hyperthermia should be referred to specialized centers for consideration of genetic and in vitro contracture testing (IVCT) to confirm their malignant hyperthermia susceptibility [63].

Differential Diagnosis

Sepsis, thyrotoxicosis, and iatrogenic overheating may resemble malignant hyperthermia during anesthesia. The measurement of end-tidal CO_2 is helpful in distinguishing malignant hyperthermia from these disorders [63].

Treatment

Discontinuation of the etiologic agent should be followed immediately by hyperventilation with 100% oxygen, administration of dantrolene, external cooling measures, and treatment of hyperkalemia. Dantrolene sodium is an inhibitor of intracellular calcium release, and is an effective antidote for malignant hyperthermia [1, 53, 63, 67]. Dosing of the dantrolene is 2.5 mg/kg as a bolus intravenous dose, repeated at 5–15-min intervals as needed to a suggested maximum dose of 10 mg/kg. Maintenance dosing at 1 mg/kg intravenously every 4–6 h should be continued for 24–72 h postoperatively [1, 53, 63]. Potential side effects of dantrolene include weakness and respiratory failure, dizziness, gastrointestinal discomfort, and hepatic toxicity [53]. Electrolyte, creatinine, transaminase, and CK levels, as well as coagulation profiles, should be followed regularly. Arrhythmias and hypertension should be treated as indicated, with careful avoidance of calcium channel antagonists [63].

Toxin-Induced Cerebrovascular Events

General Considerations

Toxin-induced stroke is uncommon; however, abuse of recreational drugs has become a risk

factor for stroke in adolescents and young adults [70]. In addition, environmental toxins and pharmaceutical agents may contribute to cerebrovascular events. Toxic mechanisms of stroke include (1) sympathomimetic vasoconstriction (cocaine, amphetamines, lysergic acid diethylamide, phencyclidine), (2) hypoxia (opioids and carbon monoxide), (3) cardioembolism (drug-induced cardiomyopathy and endocarditis), (4) vasculitis (amphetamines, cocaine, heroin), (5) enhancement of coagulation (cocaine), and (6) venous sinus thrombosis (asparaginase). In addition, there are an ever-increasing number of immunosuppressant and chemotherapeutic agents that can cause posterior reversible encephalopathy syndrome. Severe cases can result in cerebral infarction. Toxic mechanisms of hemorrhagic stroke include (1) hypertension-induced arterial rupture with or without underlying vascular malformation (cocaine, amphetamines, and phencyclidine), (2) vasculitis (amphetamines, cocaine, heroin), (3) rupture of septic aneurysm (any intravenous drug use), and (4) coagulopathy (snake venom).

Cocaine

Introduction

Cocaine, or benzoylmethylecgonine, is a weak base that is extracted from the leaves of the *Erythroxylon coca* plant. It is treated with acid to form the water-soluble salt, cocaine hydrochloride. The cocaine is then ground into a fine powder, and may be mixed with diluents that contribute bulk (talc, sugar) or mimic the effect of cocaine (lidocaine, procaine, caffeine) [71]. The hydrochloride form of cocaine may be injected, insufflated, or applied directly to oral mucous membranes. The high melting point precludes smoking of cocaine hydrochloride. The alkaloid forms of cocaine (freebase and crack) are prepared from the hydrochloride form. Although extracted by different methods, freebase and crack cocaine are the same chemical compound. Because of a lower melting point, both can be smoked [71].

Cocaine has a half-life of 30–90 min. Peak concentrations occur at 30–60 min with nasal insufflation of cocaine hydrochloride [72], and at 2–5 min with smoking of crack cocaine [73]. The major metabolites of cocaine (ecgonine methyl ester and benzoylecgonine) are pharmacologically inactive. Norcocaine, a minor metabolite produced in the liver, has pharmacologic activity similar to cocaine [71, 74]. Cocaethylene is an active cocaine metabolite that is produced in the presence of ethanol. It prolongs the clinical effect of cocaine, and accounts for the frequent simultaneous ingestion of cocaine and alcohol [75].

Epidemiology

Stroke was first reported in association with cocaine use in 1977 [76]. As abuse of stimulants has increased, so has the awareness of cocaine-induced stroke. Cocaine abuse is associated with both hemorrhagic and ischemic stroke [77]. In young adults (aged 15–44 years) with ischemic stroke, 12.1% had a history of recent illicit drug use. In 4.7%, drug use was the probable cause of stroke [78]. In a case–control study of young adults (aged 15–44 years), those admitted for stroke were more likely to abuse drugs than those admitted for other reasons (34% vs. 8%). The risk of stroke in drug abusers was 6.5 times higher than controls. In 22% of stroke patients, drug use was the probable cause of stroke. The drug most frequently used by these patients was cocaine [70].

Pathophysiology

Cocaine is a potent sympathomimetic and causes vasoconstriction via inhibition of presynaptic reuptake of norepinephrine, serotonin, and dopamine. Vasoconstriction has been observed by magnetic resonance angiography after cocaine administration and appears to occur in a dose-dependent fashion [79]. Cocaine also promotes vasoconstriction by increasing intracellular calcium release in smooth muscle cells by direct action on calcium channels, an effect that appears to be independent of cocaine's adrenergic effects [80, 81]. Blockade of fast sodium channels produces the local anesthetic effect of cocaine, and is the mechanism by which cocaine causes cardiac dysrhythmias and seizures [82].

The proposed mechanisms by which cocaine produces ischemic stroke include vasospasm,

enhanced platelet aggregation, vasculitis, and cardioembolism. Other possible causes of stroke in patients who use cocaine are related to the adulterants of illicit cocaine. Direct toxic effects of contaminants, such as lidocaine, procainamide, and amphetamines, may contribute to clinical effects. Talc and sugar are sometimes added to cocaine to increase the volume, and when administered intravenously these substances can travel as an embolus to the cerebral vasculature. Bacterial endocarditis, as a complication of any intravenous drug use, may cause ischemic stroke via embolism or hemorrhagic stroke via rupture of septic aneurysm.

Vasospasm has been identified by angiography in patients with cocaine-associated ischemic stroke [83–87]. This appears to be related to a direct toxic effect of cocaine, both by adrenergic stimulation and effect on calcium channels, although acute severe hypertension may contribute to vasospasm as well [82]. Severe vasospasm may cause focal injury to the arterial endothelium [88]. In vitro, cocaine enhances platelet response to arachidonic acid, thus promoting platelet aggregation [89]. The combination of vasospasm-induced endothelial damage and the procoagulant effects of cocaine may result in cerebral arterial thrombosis.

Cocaine use has been associated with cerebral vasculitis by angiographic findings of characteristic narrowing and dilation of arteries [90, 91]. Two cases of biopsy-proven vasculitis have been reported in associated with crack cocaine use, although one of the patients had a history of intravenous cocaine use. Angiography was normal in one case and showed multiple large vessel occlusions without characteristic vasculitic findings in the other [92]. Cocaine-associated cerebral vasculitis occurs rarely, and its diagnosis is complicated by the difficulty in differentiating vasculitis from vasospasm on angiography. Vasculitis has been reported more commonly with amphetamine use, and cocaine may cause vasculitis by a similar mechanism. However, it is important to note that cocaine products are frequently adulterated with amphetamines, so determination of etiology can be difficult.

Both acute cocaine toxicity and chronic recurrent cocaine use increase the risk of cardioembolic stroke. Acute cocaine toxicity can induce dysrhythmia or myocardial infarction [93]. Chronic cocaine use predisposes to ischemic cardiomyopathy [94]. Either of these may result in embolic ischemic stroke in the event of left ventricular thrombus formation and subsequent embolism to the cerebral vasculature.

While cocaine-induced ischemic stroke is most likely attributable to vasoconstriction, the principal mechanism of cocaine-induced intracerebral and subarachnoid hemorrhage is acute blood pressure elevation. Cocaine-induced hemorrhagic stroke may occur with or without an underlying vascular abnormality. In the presence of an aneurysm or vascular anomaly, acute hypertension causes rupture of the weak, abnormal vessel wall. In the absence of a predisposing lesion, the effect of cocaine on cerebral autoregulation likely contributes to arterial rupture. Normal cerebral autoregulation allows maintenance of constant blood flow over a range of mean arterial pressure. Above the upper limit of autoregulation, vasodilation occurs, and cerebral blood flow increases [95]. Cocaine disrupts autoregulation by lowering the upper limit of this range [96]. Thus, cocaine not only causes systemic hypertension, but also shifts the autoregulation curve such that cerebral blood flow increases at a lower mean arterial pressure. This combination increases risk for arterial rupture and intracerebral hemorrhage. This mechanism may also contribute to reperfusion injury and hemorrhagic transformation of cocaine-induced ischemic stroke.

Clinical Features/Diagnosis

The onset of stroke symptoms usually occurs within 3 hours of cocaine use [97]. The type of stroke seems to differ based upon the form of cocaine used. In a comparative study of cerebrovascular events associated with the two different forms of cocaine use, the hydrochloride form was associated predominantly with hemorrhagic stroke (intracerebral or subarachnoid). The alkaloidal form (crack cocaine) was associated with

equal numbers of hemorrhagic and ischemic strokes [86]. Cocaine has been associated with ischemic stroke in all vascular territories, as well as the retina and spinal cord. Cerebral hemorrhage may be intraparenchymal, intraventricular, or subarachnoid in location [97]. About half of patients with hemorrhagic stroke associated with cocaine have an underlying vascular abnormality [82, 83]. Therefore, it may be necessary to obtain additional neuroimaging after the acute hemorrhage has resolved.

Differential Diagnosis

As discussed above, the differential diagnosis of toxin-induced stroke includes amphetamines, PCP, LSD, opioids, and carbon monoxide. The etiologic evaluation of stroke is beyond the scope of this discussion. However, consideration should be given to obtaining urine cocaine, PCP, and amphetamine screens in addition to the usual laboratory evaluation of stroke in young adults. There are many substances that can produce false-positive results on urine PCP and amphetamine screens, and the presence of a drug or its metabolite does not prove causality. Thus, careful interpretation of urine drug screening is necessary.

Treatment

Management of acute ischemic or hemorrhagic stroke should be performed to the usual standard of care, independent of cocaine use. A retrospective review of cocaine-associated ischemic stroke patients demonstrated similar outcomes in patients who received tissue plasminogen activator (tPA) and those who did not. There were no complications related to tPA in the patients with cocaine-associated stroke [98]. Based upon this small retrospective study, it appears that tPA may be safe for patients with cocaine-associated ischemic stroke.

One exception to the usual care rule pertains to treatment of hypertension in patients with cocaine toxicity. During acute cocaine intoxication, use of beta-blocking antihypertensive agents may produce unopposed alpha stimulation, resulting in paradoxical hypertension [99]. Therefore, it is best to avoid beta-blockers in the acute setting. Benzodiazepines are often used as symptomatic management of agitation, and the subsequent decrease in sympathetic outflow results in improvement of hypertension and tachycardia [100]. If the sedating effects are acceptable, benzodiazepines are a reasonable first choice in acute cocaine intoxication.

Amphetamines

Introduction

Amphetamine is the generic term for the racemic α(alpha)-methylphenylethylamine of the phenylethylamine family. Substitutions on the phenylethylamine structure produce a variety of compounds with similar effects, including dextroamphetamine, ephedrine, methamphetamine, and 3,4-methylenedioxymethamphetamine (MDMA or ecstasy) [101].

Epidemiology

The true incidence of amphetamine-related cerebrovascular events is not known. Both ischemic and hemorrhage stroke have been reported in association with amphetamines, most often in case series of young stroke patients.

Pathophysiology

The mechanism of stroke in the setting of amphetamine use is similar to that of cocaine. Cerebral ischemia is most likely secondary to focal arterial vasoconstriction related to accelerated atherosclerosis or acute vasospasm [102]. Cerebral vasculitis has also been proposed as a mechanism of ischemic and hemorrhagic stroke, and may be a response to the amphetamine or to contaminants or diluents admixed with the amphetamine [103]. However, it is not clear if the findings in each of the reported cases represent true inflammatory arteritis, as the angiography results could also be consistent with vasospasm or multifocal stenosis. Hemorrhagic stroke induced by amphetamines is likely related to acute severe hypertension. Those with preexisting vascular malformations may be at increased risk of this complication [101].

Clinical Features/Diagnosis

Both hemorrhagic and ischemic stroke have been reported in association with amphetamines [70, 77, 104, 105], methamphetamines [102, 106], and MDMA [107–110]. Over-the-counter ephedra-like compounds (phenylpropanolamine, ephedrine, pseudoephedrine) have all been linked to stroke as well [111–115]. Hemorrhagic stroke may occur as subarachnoid or intraparenchymal hemorrhage with or without an underlying aneurysm or arteriovenous malformation. In ischemic stroke, angiography can demonstrate arterial occlusion, dissection, or vasospasm.

Treatment

The history of amphetamine use is often unavailable at the time of acute stroke care. This may be due to stroke-related deficits as well as lack of voluntary reporting of drug use. In addition, there are no clinical studies aimed at the specific treatment of amphetamine-related strokes. Therefore, the usual standard of stroke care, based upon the mechanism and location of infarct or hemorrhage, should be applied. The preferred treatment of amphetamine-related agitation, or any other sympathomimetic symptoms, is benzodiazepines.

Toxin-Induced Seizures

Introduction

Seizures are a common, serious manifestation of drug and toxin effects. Xenobiotics may contribute to seizures by (1) direct effect on electrocerebral activity, (2) induction of metabolic derangements, (3) decreased threshold in epilepsy patients, (4) withdrawal of drugs or alcohol, or (5) idiosyncratic drug reaction [116, 117]. The majority of toxin-related seizures are generalized tonic–clonic. The presence of focal or lateralizing features should prompt evaluation for an underlying lesion. The standard treatment algorithm for status epilepticus requires modification in this setting because toxin-related seizures may not respond to phenytoin [116]. Some toxins that cause seizures are associated with distinct clinical features that may guide diagnosis and treatment.

Epidemiology

The exact incidence of drug- and toxin-induced seizures is not known. A retrospective review of the California Poison Control Center database revealed 386 drug-induced seizures in 2003. The leading cause of drug-induced seizures was bupropion (23%), whereas in 1993 the leading cause was tricyclic antidepressants. Other drugs commonly associated with seizures include stimulants (cocaine and amphetamines), diphenhydramine, tramadol, antidepressants, antipsychotics, isoniazid, and withdrawal from sedatives. In this population, 68.6% had a single seizure, 27.7% had multiple seizures, and 3.6% had status epilepticus [118].

Pathophysiology

The rate of tonic firing in the cerebral cortex is a balance of excitatory and inhibitory stimuli. Excitation occurs by (1) increased sodium influx, (2) decreased chloride influx, or (3) decreased potassium efflux. Inhibition occurs by (1) decreased sodium influx, (2) increased chloride influx, or (3) increased potassium efflux [116]. A general increase in excitatory or decrease in inhibitory stimuli increases the chance of seizure occurrence.

Glutamate and glycine are excitatory neurotransmitters that cause sodium influx, resulting in neuronal depolarization. Gamma-aminobutyric acid (GABA) is the chief inhibitory neurotransmitter in the central nervous system. Its effect on the neuron is to allow chloride influx, resulting in membrane hyperpolarization. Thus, an increase in glutamate activity (e.g., ibotenic acid), a decrease in GABA activity (e.g., cicutoxin), or withdrawal of GABA agonists (e.g., ethanol, benzodiazepines) increases the incidence of seizures [117].

Histamine and adenosine increase GABA and decrease glutamate in the brain; thus, antihistamines (e.g., diphenhydramine) and adenosine antagonists (e.g., theophylline) can cause seizures [116]. Pyridoxine is a cofactor required for synthesis of GABA from glutamate by glutamic acid decarboxylase (GAD). Pyridoxine is converted to its active from by pyridoxal kinase. Inhibitors of this enzyme (isoniazid, gyromitrins, hydrazines) result in decreased GABA synthesis and refractory seizures. Toxins may also produce seizures secondary to severe metabolic derangements, including hyponatremia (MDMA), hypoxia (carbon monoxide, cyanide, hydrogen sulfide), and hypoglycemia (insulin, sulfonylureas). Table 18.2 summarizes the categories of xenobiotics that are known to cause seizures.

Table 18.2 Xenobiotics associated with seizures

Category	Xenobiotics
Antidepressants/ antipsychotics	Bupropion Lithium Olanzapine Selective serotonin reuptake inhibitors Tricyclic antidepressants
Anesthetics/ analgesics	Local anesthetics Meperidine Propoxyphene Salicylates Tramadol
Anticonvulsants	Carbamazepine Phenytoin
Stimulants	Amphetamines/MDMA Cocaine Phencyclidine
Antimicrobials	Ciprofloxacin Cephalosporins Imipenem Isoniazid
Gases	Carbon monoxide Cyanide Hydrogen sulfide
Fungi/plants	*Amanita muscaria* mushroom (ibotenic acid) *Gyromitra esculenta* mushroom (gyromitrins) Tobacco (nicotine) Water hemlock (cicutoxin)
Pesticides	Camphor Carbamates Lindane Organophosphates
Methylxanthines	Caffeine Theophylline
Withdrawal	Baclofen Barbiturates Benzodiazepines Ethanol
Miscellaneous	Diphenhydramine Flumazenil Insulin Iron Sulfonylureas

Clinical Features/Diagnosis

The associated signs and symptoms at presentation are often helpful in identifying the drug or toxin responsible for the seizure occurrence. If the seizure occurs prior to clinical assessment, it can be difficult to differentiate the effect of the seizure itself (the postictal state) with drug-induced delirium. If available, history regarding signs and symptoms prior to the onset of seizure can provide the key to the diagnosis.

Findings consistent with the sympathomimetic toxidrome, including mydriasis, tachycardia, hypertension, diaphoresis and agitated delirium, would suggest the involvement of cocaine, amphetamines, PCP, or MDMA. While the majority of toxin-induced seizures are generalized in onset, these sympathomimetics can cause intracerebral hemorrhage or ischemic stroke (as discussed above). These structural brain lesions may produce focal-onset seizures. Therefore, urgent head imaging is indicated if focal-onset seizure is suggested by the history.

Tricyclic antidepressants have multiple mechanisms of action, including inhibition of serotonin reuptake as well as blockade of fast sodium channels and muscarinic receptors. Mild tricyclic antidepressant toxicity may present with predominant anticholinergic symptoms. More severe toxicity is associated with seizures and QRS interval prolongation [119]. In fact, QRS duration longer than 100 ms is associated

with increased risk of seizures [120, 121]. Serotonin syndrome may develop, especially if tricyclic antidepressants are taken with other serotonergic medications.

The combination of coma, respiratory depression, and miosis is characteristic of the opioid toxidrome. Propoxyphene causes seizures, and because of sodium channel blockade, can result in QRS prolongation. Normeperidine, a metabolite of meperidine, and tramadol also lower the seizure threshold.

The presence of agitated delirium prior to the seizure should also suggest the possibility of drug or alcohol withdrawal. Abrupt discontinuation of GABA agonists, including ethanol, barbiturates, benzodiazepines, and baclofen, can cause a life-threatening withdrawal syndrome characterized by agitation, tremor, tachycardia, hallucinations, autonomic instability, and seizures. Ethanol withdrawal seizures are usually brief in duration; however, benzodiazepine or baclofen withdrawal is more likely to cause status epilepticus [122, 123].

Isoniazid frequently causes refractory seizures by producing a functional pyridoxine deficiency. The neurotoxin in *Gyromitra esculenta* mushrooms (false morels) is structurally similar to isoniazid, and is also associated with status epilepticus. Severe theophylline toxicity also results in refractory seizures. Seizure activity that does not respond to benzodiazepines should prompt consideration of these toxins.

Differential Diagnosis

The consideration of toxin-induced seizures should not preclude an evaluation for structural, infectious, or metabolic causes of seizure. Detailed history should be obtained to determine the circumstances and characteristics of the reported seizure in order to differentiate a generalized (from onset) seizure that may be toxin-induced from a focal-onset seizure, nonepileptic myoclonus, psychogenic nonepileptic event, or acute movement disorder (chorea, tremor, dystonia). Some toxins can cause severe muscle spasms that can mimic seizure, including strychnine, tetanus, and black widow spider envenomation. Electroencephalogram, head imaging, lumbar puncture, and laboratory studies may be necessary to confirm the diagnosis.

Treatment

A single, self-limited toxin-induced seizure may be managed with careful clinical observation without the need for long-term anticonvulsant therapy. The first step in management of prolonged or recurrent seizures is benzodiazepines. Some toxins so reliably cause seizures that prophylaxis with benzodiazepines or phenobarbital should be considered. A single dose of lorazepam has been shown to decrease the risk of seizure recurrence in ethanol withdrawal [124], whereas phenytoin does not [125]. Bupropion overdose is associated with seizures in about 30% of patients, and seizure onset may be delayed, especially with the extended-release formulation. In one study, tachycardia, agitation, and tremor were more common in patients who developed seizures than those who did not [126]. Use of benzodiazepines to treat these symptoms may prevent the delayed seizure as well. Theophylline toxicity can result in refractory seizures that are associated with increased morbidity [127, 128]. Prophylaxis with a loading dose of phenobarbital (20 mg/kg intravenously) is recommended for altered mental status, agitation, or theophylline levels of greater than 100 μ(mu)g/mL [117].

A comprehensive treatment algorithm for status epilepticus is discussed in Chap. 10: "Seizures and Status Epilepticus." For drug- and toxin-induced seizures, the first-line therapy is benzodiazepines (lorazepam), followed by barbiturates (phenobarbital) if necessary. While phenytoin is the standard second-line therapy in management of status epilepticus, it is usually not effective and may actually worsen toxin-induced seizures [129]. In general, anticonvulsants with GABA agonist properties (benzodiazepines, barbiturates, propofol) are preferred.

As discussed above, many toxins have multiple mechanisms of action and thereby cause a constellation of symptoms that may include seizures. Therefore, it may be necessary to consider

additional treatments or antidotes. For example, enhanced elimination by hemodialysis may be indicated for theophylline, salicylate, or lithium toxicity. Sodium bicarbonate is indicated for QRS widening in tricyclic antidepressant and cocaine toxicity, and for serum and urinary alkalinization in salicylate toxicity. Magnesium supplementation and potassium repletion are indicated for QTc prolongation in olanzapine toxicity. Intravenous dextrose should be administered to correct hypoglycemia secondary to insulin or sulfonylurea toxicity. In sulfonylurea toxicity, octreotide may be indicated for refractory hypoglycemia. Prolonged seizures secondary to isoniazid or gyromitrin toxicity may respond to intravenous pyridoxine supplementation (1 g for every gram of isoniazid ingested or empiric dose of 5 g). Baclofen should be restarted, in addition to benzodiazepines, for seizures related to baclofen withdrawal. Multiple-dose activated charcoal may be useful in severe carbamazepine or theophylline toxicity because of the enterohepatic recirculation of these drugs. Atropine or pralidoxime may be necessary for management of organophosphate poisoning. For assistance with management of the poisoned patient, a clinical toxicologist is available for consultation by calling the National Poison Control Center at (800) 222–1222 [116].

Toxin-Induced Acute Weakness

While toxin-induced weakness is rare, it is important to consider toxins in the differential diagnosis of both spastic and flaccid weakness, especially when the history suggests a possible exposure. Removing the source of exposure (e.g., tick paralysis) and administration of specific antitoxin may be instrumental in management. Cholinergic symptoms with or without seizures should prompt consideration of organophosphate, carbamate, or nicotine toxicity. Descending paralysis is characteristic of botulism, while ascending paralysis is the hallmark of the demyelinating polyneuropathy of diphtheria. Botulism, diphtheria, tick paralysis, and anthracenone toxicity (*Karwinskia humboldtiana*, Fig. 18.2) cause flaccid paralysis. Tetanospasmin, strychnine, and latrotoxin (black widow spider) cause severe muscle spasms. Botulism, scorpion, and Elapidae snake venom are associated with cranial nerve palsies. Table 18.3 reviews the pathophysiology, clinical features, and treatment of toxins that can produce acute weakness. Many of the antitoxins used in the treatment of arthropod and snake envenomations are associated with anaphylactoid reactions. Pretreatment with antihistamines with or without epinephrine may be considered, and immediate availability of these medications during the initial infusion is wise [130–132].

Fig. 18.2 *Karwinskia humboldtiana* (Photos courtesy of Thomas and Madonna Jones)

Table 18.3 Toxin-induced acute weakness

Category	Toxin	Mechanism of action	Source	Clinical presentation	Treatment (in addition to symptomatic and supportive care)
Synthetic compounds	Organophosphates	Inhibit AChE	Pesticides Bioterrorism (VX, sarin gases)	Cholinergic crisis (diarrhea, vomiting, bronchospasm) with fasciculations and paralysis	Atropine for muscarinic symptoms Pralidoxime for nicotinic symptoms Benzodiazepines for seizures
	Carbamates	Inhibit AChE	Pesticides		Atropine for muscarinic symptoms Consider avoiding pralidoxime due to rapid reactivation of carbamylated AChE Benzodiazepines for seizures
Bacteria	Botulinum toxin	Inhibits fusion of presynaptic ACh vesicles, prevents release of ACh	*Clostridium botulinum* – Home-canned foods – Bioterrorism	Cranial nerve palsies, followed by descending flaccid paralysis	Botulinum antitoxin Notify the health department
	Diphtheria toxin	Inhibits protein synthesis, resulting in demyelination of motor and sensory nerves	*Corynebacterium diphtheriae* – Respiratory droplets – Direct contact with skin lesions	Tonsillar pseudomembrane, followed within weeks by rapidly ascending flaccid paralysis	Diphtheria antitoxin Intravenous benzylpenicillin or oral penicillin V for bacterial eradication
	Tetanospasmin	Prevents the release of GABA and glycine from spinal interneurons by cleaving synaptobrevin	*Clostridium tetani* – Soil contamination of skin wound	Hypertonia, painful generalized muscle contractions, trismus, and increased sympathetic activity	Tetanus immunoglobulin Benzodiazepines Paralytics with ventilatory support for severe muscle spasm
Plants	Anthracenones	Decrease ATP production, resulting in Schwann cell injury	*Karwinskia* species, including *K. humboldtiana* (coyotillo)	Vomiting and diarrhea followed within weeks by ascending flaccid paralysis	
	Aconitine	Increases sodium influx via opening of sodium channels	*Aconitum* species, including monks-hood and wolfsbane	Paresthesias, followed by nausea, diarrhea, progressive weakness with bradycardia and/or dysrhythmia	Atropine may be useful for bradycardia or hypersalivation
	Strychnine	Antagonizes glycine	*Strychnos* species	Muscle spasms followed by severe generalized convulsions with intact consciousness	Benzodiazepines or Phenobarbital Paralytics with ventilatory support for severe muscle spasm
	Nicotine	Activates nicotinic ACh receptors	*Nicotiana* species, including multiple types of tobacco plant	Cholinergic crisis (diarrhea, vomiting, bronchospasm) with fasciculations and paralysis	Atropine for muscarinic symptoms Benzodiazepines for seizures

Shellfish	Saxitoxins	Inhibits sodium, calcium, and potassium channels, resulting in conduction block	*Alexandrium* species of dinoflagellate – Ingestion of shellfish	Perioral then generalized paresthesias followed by pain and paralysis with nausea and headache	Notify the health department
	Tetrodotoxin	Inhibits voltage-gated sodium channels	Vibrionaceae family of marine bacteria – Ingestion of puffer fish or Japanese shellfish – Envenomation by blue-ringed octopus	Perioral then generalized paresthesias, followed by nausea, diarrhea, and paralysis	
Arthropods	Latrotoxin	Stimulates neurotransmitter release (including ACh), resulting in vesicle depletion	*Latrodectus* species of spiders, including black widow	Diffuse muscle spasms and rigidity with hypertension, nausea, and diaphoresis	Benzodiazepines for muscle spasm Black widow antivenom for severe cases
	Ixovotoxin	Inhibits ACh release at neuromuscular junction	Ixodid and Argasid families of ticks	Ascending, flaccid paralysis	Tick removal Antitoxin used only in severe illness secondary to high risk of anaphylaxis and serum sickness
	Scorpion venom (multiple components, species specific)	Opening of sodium channels, activation of sympathetic and parasympathetic nerves, causing ACh and catecholamine release	Buthidae family of scorpions, including *Centruroides exilicauda* (bark scorpion)	Pain and paresthesias, followed by neuromuscular excitability, cranial nerve palsies, and weakness	Antivenom currently not available in the United States
Snakes (Elapidae family)	α-Bungarotoxin	Inhibits binding of ACh at nicotinic receptors	*Bungarus* species (krait)	Local swelling and nausea followed by cranial nerve palsies and paralysis	Monovalent antivenom if species is known, polyvalent antivenom if species is unknown Pressure immobilization of wound
	β-Bungarotoxin	Inhibits ACh release			
	Cobrotoxin	Inhibits binding of ACh at nicotinic receptors	*Naja* species (cobra)		
	Dendrotoxin	Inhibits potassium channels, facilitating ACh release	*Dendroaspis* species (mamba)		
	Fasciculin	Inhibits AChE			

AChE acetylcholinesterase, *ACh* acetylcholine, *GABA* gamma-aminobutyric acid, *ATP* adenosine triphosphate.

Toxin-Induced Acute Encephalopathy

Introduction

Alteration of mental status is a nonspecific finding with a very broad differential diagnosis, including many drugs and toxins. Attention to the characteristic features of the change in mentation, as well as the associated symptoms, is the key to defining possible etiologies. Alteration of cognitive function is a common side effect of many medications, even at therapeutic doses. This discussion is limited to severe poisoning resulting in agitated delirium and stupor or coma.

Pathophysiology

Because of the complex neurophysiology of the central nervous system, drugs and toxins can cause encephalopathy by a variety of mechanisms. Agents with anticholinergic, sympathomimetic, serotonergic, GABA agonist, opioid agonist, adenosine antagonist, and antihistamine effects cause varying degrees of encephalopathy. Withdrawal of GABA agonists can also produce severe encephalopathy. Environmental toxins that cause hypoxia and drugs that cause hypoglycemia result in central nervous system depression.

Clinical Features/Diagnosis

Recognition of the syndromic presentation of specific drugs and toxins can reveal the diagnosis even in the absence of exposure history. Opioid and sedative-hypnotic toxidromes cause depression of the central nervous system, resulting in stupor and coma. Sympathomimetic, anticholinergic, and withdrawal toxidromes produce agitated delirium. Cholinergic syndrome, characterized by miosis, increased secretions, diarrhea, bradycardia, and weakness, is not commonly associated with encephalopathy except when seizures occur.

Opioid poisoning causes miosis, respiratory depression, and coma. Associated prolongation of the QRS or QTc interval is suggestive of propoxyphene or methadone intoxication, respectively. Seizures in the setting of the opioid toxidrome suggest propoxyphene, tramadol, or meperidine toxicity. Reversal of symptoms with naloxone supports the diagnosis of opioid toxicity.

Sedative-hypnotic toxicity from benzodiazepines or ethanol results in sedation, and is usually associated with normal vital signs. Respiratory depression can occur when sedatives are ingested with alcohol, opioids, or other sedating medications. Methanol and ethylene glycol ingestion result in central nervous system depression, similar to ethanol toxicity, but are also associated with an anion gap metabolic acidosis. Acidosis in this setting should prompt further laboratory evaluation (serum osmolality, methanol and ethylene glycol levels), treatment with fomepizole, and nephrology consultation. Evaluation for other causes of anion gap metabolic acidosis, including salicylate toxicity, diabetic or alcoholic ketoacidosis, and lactic acidosis, should also be performed.

Sympathomimetic toxicity is characterized by mydriasis, agitated delirium, tachycardia, hypertension, diaphoresis, and hyperthermia. The most common causes of this toxidrome are amphetamines and cocaine. When hallucinations are a prominent feature, especially in the presence of nystagmus, phencyclidine intoxication should be considered. Anticholinergic syndrome also causes an agitated delirium that is similar in presentation to sympathomimetic syndrome. The distinguishing features of anticholinergic toxicity are anhidrosis, decreased bowel sounds, and garbled speech. Patients may also exhibit the picking behaviors that are characteristic of this toxidrome. Tricyclic antidepressants, diphenhydramine, scopolamine, and cyclobenzaprine are common causes of anticholinergic symptoms. Withdrawal of ethanol and benzodiazepines results in mydriasis, tachycardia, tremor, and agitated delirium. Serotonin syndrome causes an agitated delirium with autonomic instability and motor hyperactivity in the setting of serotonergic medications. This is discussed in the hyperthermic syndromes section of this chapter.

Differential Diagnosis

Metabolic derangements, central nervous system or systemic infection, cerebral structural lesions or hemorrhage, and nonconvulsive status epilepticus may all cause a general alteration of mental status. Head imaging, lumbar puncture, laboratory testing, and electroencephalography are often necessary for diagnosis. Basic chemistry profile, serum acetaminophen and salicylate levels, and electrocardiogram (ECG) can assist in determining which drugs are most likely to be involved, especially when intentional overdose is suspected and historical information is unavailable. Urine drug screening should not be routinely performed because of the high rate of false-positive and false-negative results. Care should be taken when interpreting data from these screening tests. A positive result does not prove intoxication, and a negative result does not always exclude exposure.

Treatment

Identification and discontinuation of the toxic agent, in addition to supportive care, is the mainstay of therapy for toxin-induced encephalopathy. Benzodiazepines are the recommended treatment for toxin-induced agitated delirium, including sympathomimetic, anticholinergic, withdrawal, and serotonin syndromes. Antidotes exist for opioid, benzodiazepine, and anticholinergic poisoning. The potential side effects of these antidotes should be carefully considered prior to administration.

Naloxone is an opioid antagonist that is used therapeutically and diagnostically in the setting of presumed opiate or opioid toxicity. The initial dose of naloxone is usually 0.4 mg given intravenously; however, because naloxone can precipitate severe withdrawal symptoms, a smaller test dose should be considered when opioid dependence is suspected. Additional doses may be given at 5-min intervals until neurologic and respiratory status has improved [133]. Higher doses of naloxone may be required for reversal of the synthetic opioids. The clinical effect of naloxone may be as short as 45 min [134]. Resedation may occur after naloxone reversal, especially in the setting of toxicity from methadone or sustained release opioid preparations. Patients should be observed closely for 4–6 h after naloxone administration. If resedation does occur, a naloxone infusion can be initiated at an hourly rate of two-thirds of the effective bolus dose [135]. Admission to a monitored setting is required to monitor for withdrawal symptoms or resedation.

In general, benzodiazepine withdrawal is more likely to cause complications than benzodiazepine toxicity. Benzodiazepines are not potent respiratory depressants, so reversal is not likely to prevent the need for mechanical ventilation in patients who have ingested multiple sedating medications. In polysubstance overdose or benzodiazepine-dependent patients, reversal of benzodiazepines can precipitate refractory seizures [117]. For this reason, use of the benzodiazepine antagonist, flumazenil, should be limited to pediatric poisonings or iatrogenic toxicity.

Physostigmine is an inhibitor of acetylcholinesterase that may be used for severe anticholinergic poisoning. The diagnosis of isolated anticholinergic toxicity must be clinically certain prior to administration of this antidote. Potential complications of physostigmine administration include seizures, bronchorrhea, and arrhythmias. ECG evidence of prolongation of the PR, QRS, or QTc intervals contraindicates use of physostigmine [133]. As polysubstance ingestion is common, and many anticholinergic drugs have other mechanisms of action that may predispose to seizures, the routine use of physostigmine is discouraged. Benzodiazepines are the preferred treatment for the agitated delirium of anticholinergic toxicity.

Conclusion

Toxin-induced neurologic emergencies are common. Acute encephalopathy with or without hyperthermia, stroke in young patients, unexplained seizures, and acute weakness should prompt consideration of toxicologic etiologies. Early identification of the causative toxin allows for appropriate diagnostic testing and initiation of definitive treatment.

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Substance Abuse, Somatization, and Personality Disorders

19

Ronald Kanner

Abstract

Neurologists are accustomed to dealing with difficult diseases. Our passion for deductive reasoning and the elegance of the localization process are what drew many of us to the field. When our skills in these areas fail, we become uncomfortable and assume that we are being faced with "a difficult patient." Patients with substance abuse problems, somatization/medically unexplained problems, and personality disorders fall into this category. Through a series of illustrative cases (some real and some a composite) this chapter provides insight into the emergency diagnosis and management of difficult patients who present with pain as the major complaint.

Keywords

Addiction • Borderline personality disorder • Difficult patient • Emergency management • Fibromyalgia • Malingering • Munchausen syndrome • Pseudoaddiction • Somatoform disorder • Substance abuse

Introduction

Neurologists are accustomed to dealing with difficult diseases. Our passion for deductive reasoning and the elegance of the localization process are what drew many of us to the field. When our skills in these areas fail, we become uncomfortable and assume that we are being faced with "a difficult patient." Patients with substance abuse problems, somatization/medically unexplained problems, and personality disorders fall into this category. Through a series of illustrative cases (some real and some a composite) this chapter provides insight into the emergency diagnosis and management of difficult patients who present with pain as the major complaint.

Substance Abuse

For clarity, it is best to start with a few definitions. In a consensus document [1], the American Academy of Pain Medicine, the American Pain

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Society, and the American Society of Addiction Medicine produced the following definitions:

Addiction

A primary, chronic neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving.

The term "addiction" does not appear in the index of the DSM-IV-TR. It is replaced by "substance abuse." "The essential feature of substance abuse is a maladaptive pattern of substance use manifested by recurrent and significant adverse consequences related to the repeated use of substances [2]." In the DSM-IV-TR, the criteria for substance abuse are:

A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by one (or more) of the following, occurring within a 12-month period:

1. Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (e.g., repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsion from school; neglect of children or household)
2. Recurrent substance use in situations in which it is physically hazardous (e.g., driving an automobile or operating a machine when impaired by substance use)
3. Recurrent substance-related legal problems (e.g., arrests for substance-related disorderly conduct)
4. Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of substances (e.g., arguments with spouse about consequences of intoxication, physical fights)

There are significant shortcomings in these definitions and criteria. Drug deviation and other criminal behaviors that confound treatment are not addressed, but they will be discussed later in this chapter.

Physical Dependence

A state of adaptation that is manifested by a drug class-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist [1].

Tolerance

A state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time [1].

Drugs and alcohol are present in 49% of emergency room visits [3]. Prescription drug abuse involves the use of the medication, usually by self-administration, in a manner that deviates from medical, legal, and social standards [4]. Abuse of prescription drugs is on the rise [5] and, in the United States, marijuana is the only drug more abused than prescription medications [6, 7]. Internet sites offer doctor consultations for $120 and state, "We are an online pharmacy that specialize [sic] in chronic pain medication, we use only licensed US doctors and pharmacy's [sic], Medications can be prescribed and shipped within 24–48 h, you simply call the doctor at the time that suites [sic] you, our friendly doctor will prescribe anything that he feels necessary that is suitable for your condition" [8].

Given this setting, it is not surprising that physicians must make difficult decisions regarding opioids in the emergency room. We are often called to see patients in severe pain and, explicitly or implicitly, asked the following questions:

1. Is this patient a substance abuser who is seeking opioids?
2. Is it reasonable and safe to continue this patient on opioid medications if he/she is already taking them?
3. What is the relative risk of opioid abuse should I decide to start this patient on opioid medication for chronic pain?

Case #1

A 45-year-old man presents to the emergency room with severe low back pain. He states that he had an injury some 4 years ago and has required increasing doses of opioid medications to keep his pain under fair control. Over the past week, he states that he has had a marked increase in his pain and his opioid intake. He states that he is currently taking 80 mg of a slow-release oxycodone product every 8 h, with supplemental doses of 15–30 mg every 2–3 h. On examination, he is awake, alert, and oriented. He is aggressively demanding medications. His pupils are 4 mm and reactive. The rest of his neurological examination is normal. Urine toxicology is negative for opioids, but positive for cocaine.

On a first visit, it is often difficult to determine whether or not there is a significant abuse issue. In this case, it is fairly straightforward. Pupillary constriction and constipation are the two opioid side effects to which tolerance rarely develops. The fact that he states he is on a high dose of opioids but maintains large pupils and a negative urine screen indicates that he is diverting the drug. The presence of an illicit substance in the urine is also diagnostic of substance abuse.

Confronting the possibility of substance abuse must be done with tact and support. Violence is not uncommon in emergency departments [9] and patients with acute and chronic pain may report violent ideation against physicians [10]. The guidelines discussed are focused on providing the best and safest care for the patient, while maintaining the safety and ethics of the physician.

In a 1999 publication entitled "Don't Be Scammed by a Drug Abuser" [11], the Drug Enforcement Administration (DEA) listed the following as "common characteristics of the drug abuser":

- Unusual behavior in the waiting room
- Assertive personality, often demanding immediate action
- Unusual appearance—extremes of either slovenliness or being overdressed
- May show unusual knowledge of controlled substances and/or gives medical history with textbook symptoms or gives evasive or vague answers to questions regarding medical history
- Reluctant or unwilling to provide reference information. Usually has no regular doctor and often no health insurance
- Will often request a specific controlled drug and is reluctant to try a different drug
- Generally has no interest in diagnosis—fails to keep appointments for further diagnostic tests or refuses to see another practitioner for consultation
- May exaggerate medical problems and/or simulate symptoms
- May exhibit mood disturbances, suicidal thoughts, lack of impulse control, thought disorders, and/or sexual dysfunction
- Cutaneous signs of drug abuse—skin tracks and related scars on the neck, axilla, forearm, wrist, foot, and ankle. Such marks are usually multiple, hyperpigmented, and linear. New lesions may be inflamed. Shows signs of "pop" scars from subcutaneous injections

While these recommendations may provide some guidelines, they are not scientifically proven. They are more applicable to a private office visit than they are to an emergency room. However, with some adaptation, they are probably useful. It is the responsibility of the physician

to perform and document a thorough history and physical examination, commenting on whether or not there is a discernible cause for the pain and whether or not there are signs and symptoms indicative of substance abuse. The DEA further suggests:

- Document examination results and questions you asked the patient.
- Request picture I.D., or other I.D., and Social Security number. Photocopy these documents and include in the patient's record.
- Call a previous practitioner, pharmacist, or hospital to confirm patient's story.
- Confirm a telephone number, if provided by the patient.
- Confirm the current address at each visit.
- Write prescriptions for limited quantities.

Case #2

A 38-year-old woman with lupus presents with severe back pain. She has been on steroid therapy for proximally 1 year and plain films of the spine demonstrate osteoporotic fractures at T-10 and L-2. She readily relates a history of intravenous opioid abuse in her teens, but states that she has been clean and sober for the past 20 years.

The most difficult scenario arises when a patient who has current or previous substance abuse problems presents with a severe pain syndrome. The natural tendency is to avoid prescribing opioids. However, there may be circumstances in which the use of opioids is not completely contraindicated. The crucial issue is to create a therapeutic regimen that is safe for both the patient and the physician. Portenoy et al. [12] suggest categorizing substance abusers into three broad groups that have relatively different risks for aberrant behavior. First, patients who are in a period of drug-free recovery may present more of a problem with undertreatment than with abuse. Physicians may be reluctant to prescribe opioids in settings that truly require them, such as trauma or the postoperative period. The decision for long-term therapy is not one that would necessarily be made on an emergency basis.

Case #3

A 58-year-old woman with metastatic breast cancer involving the spine and hip has a history of opioid abuse, but is currently in a methadone treatment program. She takes 60 mg of methadone per day and has been cooperative with the program. Urine drug screens have routinely been negative for any illicit substances. She currently has severe pain in the spine and hip, but a completely normal neurological examination.

Portenoy's second group is patients who have a history of opioid abuse but are currently enrolled in the substitution therapy program. They present a difficult pharmacological problem. These patients will often require a higher dose of opioid than would be needed in the opioid-naïve patient. One guideline would be to provide the opioid substitution medication at a constant level, then provide appropriate dosing on top of the baseline. If the decision is made to use methadone for analgesia, the regimen is significantly different than the regimen used for avoiding an abstinence syndrome. For the latter, a single daily dose is sufficient. However, for pain management, most patients require much more frequent dosing, up to every 4 h. It is very difficult to judge whether increased pain complaints are due to the prior addictive behavior or to truly increased pain. Hospitalization may be required to manage these patients adequately. Before undertaking a course of opioid analgesic therapy in a patient on maintenance therapy, there must be adequate communication between the treating physician and the physician managing the opioid maintenance.

The third group, patients with ongoing abuse, represents a diverse population. However, given the medical and psychiatric comorbidities, there is a very great risk that even the best intended treatment with opioids would be undermined.

Case #4

A 20-year-old man with sickle cell disease and recurrent sickle cell crises presents with severe knee and abdominal pain. He is writhing on a

stretcher and demanding parenteral meperidine. He has taken oxycodone/APAP at home, with partial relief. His parents state that he will occasionally take an extra dose at bedtime or late at night. When questioned, he admits that it "calms him down." On two occasions, he has requested refills of his medications before the allotted time.

Patients already taking opioid analgesics for painful problems represent a different group. Aggressive complaints about the need for higher doses of drug often raise a physician's suspicion that the patient is an abuser. However, it may simply be a sign of anxiety over being able to obtain sufficient relief, because of prior experience with inadequate dosing, so-called pseudo-addiction [13]. Requesting a specific drug may simply indicate familiarity with the drug and its effects. Other behaviors that raise suspicions about the possibility of abuse, but are not necessarily indicative of abuse, include drug hoarding during periods of reduced symptoms, acquisition of similar drugs from other medical sources, unapproved use of the drug to treat other symptoms (such as anxiety or insomnia), unsanctioned dose escalations, reporting psychic effects not intended by the clinician, and requesting specific drugs [14].

Case #5

A 42-year-old man with severe rheumatoid arthritis has been managed on sustained-release morphine 120 mg every 8 h. He frequently calls on Friday evenings, when a different physician is covering, to state that he lost his prescription and needs a refill. He admitted obtaining oxycodone from a friend, because the pain had become too intense. After a recent car accident, he was found to have alcohol, oxycodone, and morphine in his urine.

Even in patients with painful medical illnesses requiring opioids, aberrant behavior can occur. Some of the signs include prescription forgery, concurrent abuse of related illicit drugs, recurrent prescription losses, selling prescription drugs, multiple unsanctioned dose escalations, stealing or borrowing another patient's drugs, and obtaining prescription drugs from nonmedical sources [15]. "Problematic" substance use is more likely to occur in patients with a prior history of addiction, those with significant psychiatric comorbidity, and those with a history of sexual or physical abuse [16].

Case #6

A 56-year-old man with psoriatic arthritis has been unresponsive to nonsteroidal anti-inflammatory drugs and to disease-modifying agents. He has never tried opioid analgesics, but is quite dissatisfied with his current pain management. The fingers show sausage-like deformities, there are psoriatic patches on both elbows and shins, and he appeared quite distressed. He rates his current pain as 7/10. There is no prior history of substance abuse and his neurological examination is normal. Is it reasonable to commence opioid therapy in this patient who is likely to require it for a long time?

"Optimal methods to predict risk of aberrant drug-related behaviors before initiation of opioids for chronic noncancer pain and to identify aberrant behaviors after therapy is initiated are uncertain [17]." There are a number of screening tools that have been used. The Screener and Opioid and Assessment for Patients with Pain (SOAPP) is a self-administered test that contains questions regarding feelings of impatience with doctors, preoccupation with supply of medication, frequent mood swings, and a number of other items that may help a physician to understand how closely a patient will need to be monitored for abuse [18]. It has not been studied in an emergency room setting and is probably more appropriate for office practice. Passik [19] has provided an intelligent overview of the screening tools available and the assessments needed before initiating opioid therapy for chronic pain of noncancer origin. Ease of administration and appropriateness for the individual patient and setting are the primary guides. If the decision is made to start opioid therapy, it is the responsibility of the

prescriber to perform due diligence to be in compliance with the regulatory issues and State Medical Board rules [19]. It is the obligation of the prescriber to document the decision and to obtain informed consent. A treatment strategy must be agreed upon between the patient and the prescriber and it should be documented in the chart. Risk stratification for aberrant drug-taking behavior is not foolproof, but can be broadly estimated to be low, moderate, or high, based on the risk factors cited above. Ongoing measures to assess aberrant behavior are advisable [19, 20]. Even if opioid therapy is started and aberrant behavior occurs, there is no obligation on the part of the prescriber to continue therapy. An "exit strategy" should be developed in the eventuality of abuse [21]. Follow-up and documentation are the key issues.

Somatization

Case #7

A 44-year-old woman is in the emergency room because of debilitating, widespread pain. She demonstrates severe tenderness to touch in both supraspinatus muscles, the glutei, near the sacroiliac joints, in the strap muscles of the neck, and in the medial knee pads. She complains of chronic fatigue, headache, irritable bowel syndrome, vulvodynia, and multiple chemical sensitivities. She also had an unexplained episode of left-sided weakness and sensory loss, which resolved spontaneously.

Somatization, hysteria, conversion disorder, and Briquet's syndrome are terms that are often used interchangeably. Most commonly, conversion disorders present as neurological dysfunction, involving motor loss, sensory loss, or cognitive changes. True somatization disorder, as defined by the DSM-IV-TR [2], is a rather unusual presentation. It involves a history of many physical complaints beginning before age 30 that occur over a period of several years. The symptoms result in treatment being sought or significant impairment in social, occupational, or other important areas of functioning. It requires four different areas of pain, two gastrointestinal symptoms, one sexual symptom, and one pseudoneurological symptom. On the other hand, the *process of somatization* can be more broadly conceptualized as the expression of stress or emotional problems in terms of physical symptoms. The key point is that these symptoms are not intentionally produced. They are not an attempt to deceive, but an expression of psychological distress.

Katon and Walker [22] estimated that "14 common physical symptoms are responsible for almost half of all primary care visits. Only about 10%–15% of these symptoms are found to be caused by an organic illness over a 1-year period. Patients with medically unexplained symptoms are frequently frustrating to primary care physicians and utilize medical visits and costs disproportionately." As many as 50% of new patients referred to a neurologist have at least one medically unexplained symptom, and many of them meet criteria for somatoform disorder [23]. These are the "difficult patients" [24], any one of which can ruin a neurologist's day [25] and who are poorly managed by many physicians [26].

Fibromyalgia embodies many of the characteristics of a somatization disorder. Its etiology remains unclear, its clinical manifestations are protean, management is difficult, and psychological factors are often important [27]. Aaron and Buchwald [28] view fibromyalgia as one of the "unexplained clinical syndromes." The authors state that "…physicians for at least a century have described illnesses seen in clinical practice that share features such as fatigue and pain, disability out of proportion to physical examination findings, inconsistent demonstration of laboratory abnormalities, and an apparent association with "stress' and psychosocial factors." These clinical features, as well as clinician discomfort with making a diagnosis in the absence of objective abnormalities, have resulted in the creation of disturbing labels for affected patients, such as "heart sick patients," "hypochondriacs," and "amplifiers." The patients' symptoms and syndromes have been called "functional," "somatic," "medically unexplained," and

"psychosomatic"[29]. The diagnosis given to a specific patient may depend more upon the specialty of the physician consulted than on the chief complaint. What may be needed is "a paradigm shift in which unexplained symptoms are remedicalized around the notion of a functional disturbance of the nervous system and treatments currently considered "psychiatric" are integrated into general medical care" [29]. Dworkin and Fields [30] have even suggested that fibromyalgia may be considered from the point of view of neuropathic pain. The notion that physical and emotional issues require a dichotomous choice may be difficult to maintain [31]. Crombez et al. [32] reviewed 1,020 studies mentioning somatization (or a similar term) published between 1989 and 2007. They chose 1989 because that was the year after the publication of Lipowski's paper defining the concept and its clinical application [33]. They concluded that "The current operational use may unduly lead to 'psychologization' of physical complaints." In that same issue, Merskey [34] editorialized that in regard to somatization, "[there was] little justification for it as used over the 40 years since the definition appeared." However, lack of proper use is not proof of failure of concept.

In the emergency department, however, such theoretical distinctions rarely come into play. Recognition of multiple symptoms is the key. Patient satisfaction is not just a function of pain relief. Although it may be difficult to get patients to focus on individual symptoms, quality-of-life issues, such as fatigue, sleep disturbance, and appetite changes, must be addressed. Planning for a coordinated approach to symptom management can be started at the initial consultation. It should include exercise, psychological therapies, and a well-reasoned pharmacological plan.

Emergency room patients with somatic pain complaints and no physiological cause can be divided into two broad categories: those with symptoms and signs consciously synthesized for secondary gain and those in whom the symptoms are the unconscious expression of psychological disorders [35]. The latter were addressed above, and the former will be addressed below.

Malingering

Case #8

A 35-year-old man has had multiple emergency room visits for severe leg pain and dysuria. Urinalysis demonstrated gross hematuria onto prior visits and he was treated with intravenous hydromorphone. He left the hospital before an intravenous pyelogram could be performed. He returns, complaining of the same pain. After giving a urine sample, he is noted to have a small cut on his index finger.

Malingering is a conscious effort to deceive. It involves "the intentional production of false or exaggerated symptoms motivated by external incentives, such as obtaining compensation or drugs, avoiding work or military duty, or evading criminal prosecution. Malingering is not considered a mental illness" [35], but it can occur in the setting of mental illness, particularly in personality disorders. Suspect behaviors include a medicolegal presentation, marked discrepancy between the claimed distress and the objective findings, lack of cooperation during the evaluation, and the presence of antisocial personality disorder [34]. In the emergency department, the most common goals of malingering are obtaining drugs or obtaining shelter. In a physician's office, disability claims or monetary compensation are the primary goals.

Some diagnostic clues to malingering include an evasive attitude toward the examiner and hostility. Although the thought process is marked by preoccupation with the claimed illness, it is usually cogent. Threats of violence or suicide may follow a challenge to the veracity of the claim [20, 36]. The differential diagnosis of malingering includes somatoform disorders, hypochondriasis (the persistent conviction that one is or is likely to become ill, often involving symptoms when illness is neither present nor likely, and persisting despite reassurance and medical evidence to the contrary), factitious disorders, and, of course, a missed medical diagnosis.

Because malingering is neither a medical nor psychiatric illness, treatment is not straightforward. It is probably advisable to avoid direct confrontation, as that is most likely to lead to hostility

and a breakdown of any ability to approach the patient. Temporizing with psychiatric consultation may be helpful, but malingering behavior is likely to persist "as long as the desired benefit outweighs the inconvenience or distress of seeking medical confirmation of the feigned illness" [33].

Munchausen Syndrome (Factitious Disorder)

The difference between Munchausen syndrome and malingering is that the feigned symptoms do not produce secondary gain [37]. Assumption of the sick role is the goal in itself. Patients may go to extraordinary lengths to produce signs and symptoms of painful or life-threatening illnesses [38, 39]. The DSM-IV TR [2] lists the following diagnostic criteria:

1. Intentional production or feigning of psychological or physical signs or symptoms
2. Assumption of the sick role as motivation for the behavior
3. Absence of external gain, such as avoiding legal responsibility or improving physical well-being, as in malingering

Behaviors that should raise the suspicion of Munchausen's include pathological lying (*pseudologia fantastica*), peregrination (traveling or wandering), and recurrent, feigned or simulated illness [40]. Treatment involves curing whatever harm the patient has inflicted on himself/herself, followed by initiation of psychiatric therapy. Unfortunately, the issues are often so embedded in a personality disorder that the patient will leave the hospital before psychiatric treatment can occur [40].

Personality Disorders

A personality disorder is an enduring pattern of inner experience and behavior that deviates markedly from the expectations of the individual's culture, is pervasive and inflexible, has an onset in adolescence or early adulthood, is stable over time, and leads to distress or impairment [2]. These are fairly common disorders, affecting up to 6% of the general population [41] and nearly half of the psychiatric population [42].

Three clusters are identified, based on descriptive similarities:

1. Odd and eccentric behavior, which is characteristic of the paranoid, schizoid, and schizotypal disorders
2. Dramatic, emotional, and erratic behaviors, which are characteristic of histrionic, narcissistic, borderline, and antisocial behaviors
3. Anxious or fearful behaviors, which are characteristic of avoidant, dependent, and obsessive–compulsive disorders [43].

Although 11 subtypes are listed, the borderline, histrionic, obsessive–compulsive, and dependent personality disorders are the ones that are most likely to cause problems in pain management [44]. Small reviews [45] have suggested a very high prevalence of personality disorders in patients with chronic pain, but others [46] have suggested that the pain itself may influence the assessment of personality disorders.

Patients with borderline personality disorder show a pattern of instability in interpersonal relationships, self-image and affect, and marked impulsivity [2]. Some of this impulsivity can lead to self-injurious behavior that may even have a neurobiological substrate [47]. The combination of chronic pain and abnormal behavior can affect the physician and patient relationship and lead to a poor therapeutic outcome [48]. Furthermore, patients with comorbid personality disorder associated with another diagnosis are less likely to respond to standard treatments [43]. Treatment of the borderline personality disorder (and, indeed, most personality disorders) is certainly beyond the scope of practice of a physician in an emergency situation. However, there are useful tools for recognizing and assessing the patient in the emergency room and for planning for future management.

Clues to the diagnosis of personality disorder include the observation of frequent mood swings, angry outbursts, difficulty in delaying gratification, and externalizing and blaming the world for their behaviors and feelings [43]. Confrontation is never successful and there are no medications approved for the treatment of personality disorders. However, a case can be made for assessing the particular personality style (or disorder) and creating a conversation that addresses the salient points of that disorder and empowers the patient to save face, as suggested by Fortin [24]:

- With an obsessive patient, compliment him on his intellectuality, precision, and organization; avoid battles over control or pushing the patient for much emotion which these patients usually like to avoid.
- With a dependent patient, the relationship is enhanced by meeting some of his special needs and not pushing him to be independent; over time, as the relationship is established, the clinician wants to facilitate the patient's more independent functioning.
- For the histrionic patient, the clinician can compliment him upon his flair, uniqueness, fun-loving nature, and attractive clothing and not use as much intellectual discussion as with an obsessive patient.
- For the self-defeating patient, the relationship is enhanced by simply acknowledging his plight and not trying to fix the situation.
- For the patient with borderline personality disorder, empathic acknowledgment of abandonment fears coupled with clear limit setting is an important part of the treatment plan.

The conceptual model of "vulnerability-diathesis-stress" can be useful in the assessment of the patient with chronic pain [49], as well as in the patient's psychopathology [50]. As physicians, we must alter our structural model of purely biological diagnosis in order to deal more compassionately and effectively with patients who have pain, substance abuse issues, somatization issues, or personality disorders. In all of the emergency room encounters, it is of paramount importance to document an appropriate history and physical examination, rationale for diagnostic/therapeutic decisions, and appropriate follow-up.

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