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Manifestations of Stroke

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Manifestations of Stroke

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Preface

What is a stroke? The latest definition by WHO is simply stated as 'a rapidly developing loss of brain function(s) due to disturbances of the blood supply to the brain'. Within this definition lies a wide variety of symptoms and signs that clinicians sometimes fail to detect. In fact, it is believed in the collective imagination and by many physicians that stroke is solely characterized by a loss of strength, language disturbances, and vertigo and/or sensitivity loss which lead to varying degrees of disability. Currently, emergency stroke management depends heavily upon stroke scores to quantify the damage and to speed up the diagnosis process. In fact, stroke management presently requires determining time of onset, the presence of vessel occlusions, in order to decide on thrombolysis treatment. Moreover, the development of high-resolution neuroimaging technologies has become the 'third' clinical eye of physicians. These are the hallmarks of acute stroke treatment, which are light-years away from the typical academic discussions we had with our mentors which focused on the question 'Where are the lesions'? Unfortunately, several important stroke syndromes are not taken into consideration in these currently used stroke scores and for this reason they tend to be overlooked and not treated. In the 21st century neurologists need to reach a compromise between contemplative neurology and current emergency stroke medicine. In this regard, every chapter deals with the principal clinical pictures of stroke syndromes in order to provide present and future stroke physicians a 'snapshots handbook'. Being so, the aim of this work is to provide an overview on current stroke syndromes which together with stroke scores will lead to more thorough assessments in emergency settings.

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Motor Syndromes

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Abstract

Motor disturbances alone or associated with other focal deficits are the most common symptoms suggesting a neurovascular event. An appropriate clinical assessment of these signs and symptoms may help physicians to better diagnose and to both better treat and predict outcome. In this paper the main clinical features of motor deficit are described together with other motor-related events such as ataxia and movement disturbances.

During the first evaluation of conscious patients with a suspicion of stroke, the initial steps should include an assessment of motor performance as well as impairment. Regarding the latter, its distribution and whether it is isolated or not need to be accurately determined. We urge assessing the movements in each of the limbs while at same time looking for any spontaneous movements and asymmetries. When the patient is unable to cooperate we suggest eliciting movements with painful stimuli (sternum, inner end eyebrow, squeezing nail bed of a digit in each limb).

Most motor deficit profiles in stroke patients (75%), according to many studies, are characterized by uniform weaknesses of the hand, foot and hip [1, 2]. Other neurological conditions which need to be ruled out include: neglect, ataxia, apraxia and/or anosognosia. These groups of conditions may result in varying motor performance without any direct damage to the corticospinal structures. The main clinical patterns of motor syndromes, together with their probable topographic locations, are reported in table 1.

A faciobrachial motor weakness pattern is usually seen in events involving the superficial branch of the middle cerebral artery (MCA), while monoparesis may be more often observed in smaller infarcts of the cortex and centrum ovale [3]. Non-lacunar etiologies of stroke (large artery disease and cardioembolism) are the main causes of stroke not involving lower limb motricity.

The weakness distribution found in capsular or brainstem strokes reminds us of the local somatotopic motor pathway organization. The internal capsule leg-directed fibers can be found more dorsolaterally while the arm-directed fibers lie ventromedially. A proximal-distal clinical correlate in motor deficit patterns is the effect of the gradient in the corticospinal tract descending down the spinal cord. Specific motor deficits more often involve the axial musculature than intrinsic limb musculature. A mostly proximal limb paresis is more often observed in infratentorial lesions while the distal limb weakness pattern is more often characteristic of supratentorial events, and these two have different prognostic effects [4].

A relevant number of stroke victims develop a faciobrachial weakness without any involvement of the lower limb. This is generally due to

Table 1. Motor syndromes and more frequent vascular event location

Segmental weakness	Stroke location	Arterial territory
FUL	Deep infarct	MCA
FU	Superficial infarct	MCA
UL	Variable	ACA/VB
U	Superficial/deep	MCA/watershed
L	Superficial	ACA
F	Superficial/deep	MCA/VB

F = Facial; U = upper limb; L = lower limb; MCA = middle cerebral artery; ACA = anterior cerebral artery; VB = vertebrobasilar.

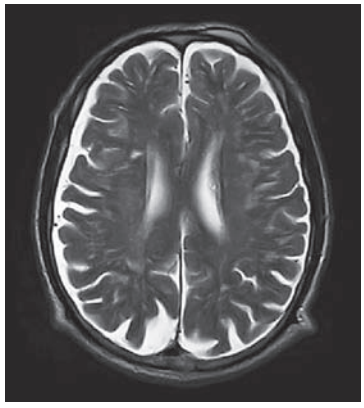

Fig. 1. Magnetic resonance study (T_2-weighted sequences) in a patient suffering from a minor lower facial paresis. The study demonstrated a new ischemic lesion in the supratentorial right hemispheric white matter.

an involvement of the MCA territory, but even if less frequent it can be seen also in basal ganglia and rarely in anterior cerebral artery (ACA) and brainstem infarctions.

A pure motor hemiparesis was first reported in the autopsy studies by Fisher in the 1960s and such clinical presentations later led to the development of the 'lacune' concept [5]. Taking into account various hospital-based registries, the prevalence of this clinical picture has been reported to be between 9 and 24% [1, 5, 6].

An isolated monoparesis is a rare symptom in stroke patients, around 1–2% of cases, and is often caused by either small artery disease or small hemorrhages [7]. Lower limb isolated distal weakness has also been reported to be associated with cortical infarcts [8].

An isolated facial paresis with abrupt onset and no clear involvement of limb motricity is an uncommon finding, generally due to damage of the internal capsule genu. Furthermore, strokes involving the corona radiata have been reported to lead to lower face palsy triggered by upper motor neuron damage (fig. 1). A larger facial paresis including the upper face may be found in pontine events. Such clinical presentations, when mimicking a partial Bell's palsy, from a diagnostic point of view are challenging for stroke physicians [9].

When motor syndromes are associated with an overlapping sensory loss the topography of the stroke is expected in the internal capsule. This is true also if an ataxic disturbance of the paretic limb is reported (ataxic hemiparesis), together with a pontine or corona radiate topography.

A segmental weakness involving contralateral limbs (without facial involvement) may be caused by ACA infarctions. While a distal leg predominant deficit associated with ACA events has been observed in 25% of cases. The ACA supply territory if damaged may lead to mono- or bilateral medial frontal damage and thereby provoking disturbances to upper extremities including bimanual weakness and lack of coordination.

Movement Disorders and Ataxia

Hypo- or hyperkinetic movement disorders may occur in acute stroke of which the more frequent forms include hemichorea and hemiballism.

In hypokinetic disorders related with stroke, vascular parkinsonism is the most widely reported even if this clinical entity is still a debated. While the clinical picture of an atypical parkinsonism is

usually associated with multiple vascular damage to neuroimaging, being so the condition of vascular parkinsonism should be ruled out. Any lack of response to standard antiparkinsonian drugs renders it difficult to distinguish between extrapyramidal disturbances such as those included in the group of multiple systemic atrophies. Other conditions even more rarely reported include: asterixis, dystonia, tremor and myoclonus [10, 11]. Usually, hyperkinetic stroke-related disturbances are transient and more often related to either basal ganglia or thalamic damages.

Ataxic disturbances have generally been reported in vascular cerebellar damage cases or those involving the cortico-ponto-cerebellar and/or dentate-thalamic pathways [12]. According to the traditional features of cerebellar structures, (i) archicerebellum, (ii) paleocerebellum and (iii) neocerebellum as parallel syndromes are useful. While the vermian involvement leads to both head and trunk-postural ataxia, an anterior lobe stroke will result in ataxia of stance and gait. Any damage of the cerebellar hemisphere is correlated with a major hypotonic compromise of limb movements, with asynergia and/or dysdiadochokinesis, as long as it is not associated with a concurrent weakness that may impede any movement analysis.

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Sensory Syndromes

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Abstract

Somatosensory deficit syndromes represent a common impairment following stroke and have a prevalence rate of around 80% in stroke survivors. These deficits restrict the ability of survivors to explore and manipulate their environment and are generally associated with a negative impact on quality of life and personal safety. Sensory impairments affect different sensory modalities in diverse locations at varying degrees, ranging from complete hemianesthesia of multiple modalities to dissociated impairment of somatosensory submodalities within a particular region of the body. Sensory impairments induce typical syndromal patterns which can be differentiated by means of a careful neurological examination, allowing the investigator to deduce location and size of the underlying stroke. In particular, a stroke located in the brainstem, thalamus, and the corticoparietal cortex result in well-differentiable sensory syndromes. Sensory function following stroke can be regained during rehabilitation even without specific sensory training. However, there is emerging evidence that specialized sensory interventions can result in improvement of somatosensory and motor function. Herein, we summarize the clinical presentations, examination, differential diagnoses, and therapy of sensory syndromes in stroke.

Perception and interpretation of somatosensory information is a general requirement for human life. Mental registration and interpretation of sensory stimuli is dependent on information from several sensory systems. Hence, the somatosensory network is closely interlinked to all other sensory structures, including the higher functional areas in the brain, and the motor system. Due to this tight relationship, somatosensory function is not only susceptible to damages to somatosensory brain areas, but also vulnerable to impairments of other brain systems. Accordingly, most stroke survivors suffer several somatosensory deficits (body senses such as touch, temperature, pain, and proprioception). Reported prevalence rates appear to vary between 65 and 100% [1–4]. Even in patients diagnosed with pure motor stroke via neurological examination, sensory dysfunction was found in 88% of cases [3]. Impaired sensory function is often notably underdiagnosed, though it hinders the ability to explore and manipulate one's environment and negatively affects the quality of life as well as personal safety. Therefore, correct diagnosis and appropriate treatment of sensory syndromes has raised much attention in recent years.

Clinical Presentations

Stroke affects one or more of the sensory modalities in varying degrees, ranging from complete hemianesthesia of multiple modalities to dissociated impairment of somatosensory submodalities within a particular body region.

Studies report an impairment of elementary sensory modalities such as touch, pressure, pain, vibration, and temperature in 53–64% survivors after stroke [2]. Impaired proprioception occurs at a similar frequency [2, 5]. Moreover, the majority of studies consistently regard stereognosis (tactual object recognition) as being the most common somatosensory impairment following stroke [2, 6]. However, pure or predominant somatosensory symptoms in stroke patients are also not uncommon. These are reported as representing the most frequent lacunar syndromes [7–9]. In most cases, the lacuna was found in the thalamus [10–12], but also brainstem [13, 14], capsular [15], and parietal [6] lesions are described as causing predominantly somatosensory symptoms. The degree of impairment of sensory function correlates closely to stroke severity (NIHSS score) and extent of lesion [2, 5]. In contrast, larger strokes almost always result in non-sensory symptoms due to the tight relationship of the somatosensory network to other systems.

Although somatosensory impairment varies widely according to location of stroke within the CNS, the investigator can suspect stroke site via particular patterns of presentation:

Sensory impairment due to brainstem stroke results mostly from small infarcts or hemorrhages in the medulla or pons. Lateral brainstem strokes in medulla and pons often cause a loss of pain and temperature sensation. Most lateral, they affect the ipsilateral face and the contralateral lower body (type I of Stopford's classification [16]). Mediolateral lesions can affect only the upper part of the body (type II), while large strokes in both of these regions can result in a combination of crossed and unilateral pattern (type III).

Paramedian infarcts are found more frequently in the pons than in the medulla and affect elementary sensations (most often vibration and position sense) and often show dominance in the cheiro-oral or leg region. Somatosensory symptoms of the facial or perioral region due to paramedian pons lesions frequently occur bilaterally. Aside from sensory deficits, most patients also suffer dizziness and gait ataxia [13].

Sensory impairment owing to thalamic stroke is predominantly caused by lacunar infarcts in the ventroposterior nucleus of the thalamus, again mostly affecting elementary sensations showing a faciobrachiocrural distribution. A typical constellation of symptoms for thalamic strokes include numbness and paresthesia, although dysesthesia and pain also commonly occur. The latter can develop directly following stroke, or subacutely a few days later (2–15 days) [12].

Corticoparietal stroke mainly involves discriminatory modalities of sensation like proprioception, stereognosis, or texture recognition which are usually limited to one or two parts of the body, sparing the trunk [6, 17]. In particular, a combination of impaired discriminating modalities with a preserved vibration sense can be considered as being characteristic for cortical strokes [6]. Since this pattern arises mainly due to lesions in the superior-posterior parietal cortex, it is referred to as the cortical sensory syndrome. However, a lesion in the inferior-anterior parietal cortex (parietal operculum, posterior insula) can mimic a thalamic sensory syndrome and is designated as the pseudothalamic syndrome [6]. A corticoparietal stroke resulting in a pseudothalamic syndrome cannot be differentiated from a thalamic stroke on the basis of sensory deficits alone. In cases of left hemispheric parietal strokes, neuropsychological dysfunctions usually involve language impairment, while right hemispheric lesions lead to visuoconstructive and visuospatial disturbances [6, 18–20]. In addition, somatosensory impairment due to cortical strokes is accompanied by some motor dysfunction in over 90% of cases [21].

Somatosensory impairment is more frequent in right hemispheric than in left hemispheric stroke [22]. Several studies report significant sensory impairment of the ipsilateral body side with an incidence of 17% following unilateral stroke [2, 3, 23]. The border zone of sensory symptoms on

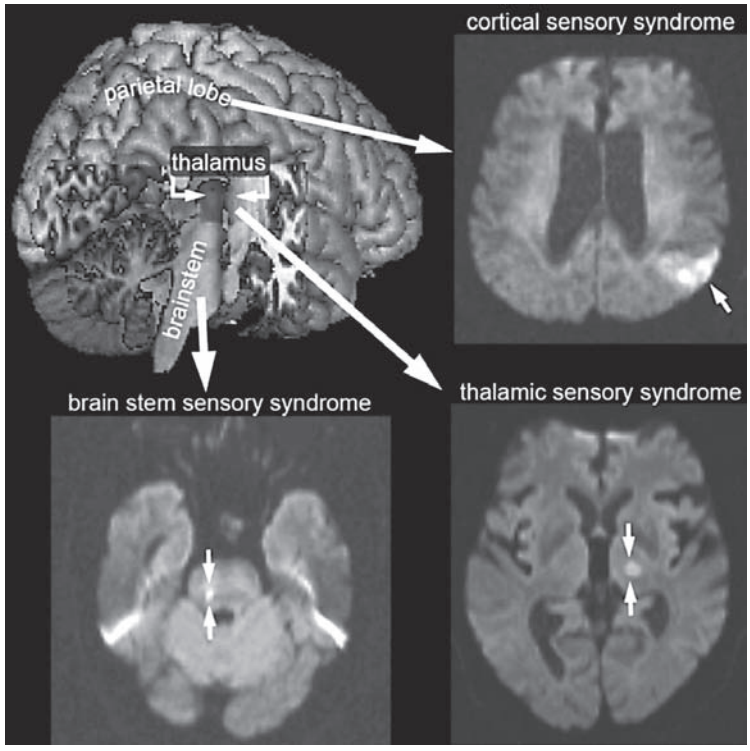

Fig. 1. MRI lesion examples (diffusion-weighted imaging) for different sensory syndromes.

the trunk and face are expected to be paramedian due to the 1–2 cm sensory function overlap of the intercostal nerves (fig. 1).

Diagnosis of Somatosensory Syndromes

Study results pertaining to the occurrence of somatosensory impairments after stroke vary widely [1, 2, 4, 24]. It is thought that the incidence is often underestimated since differential sensory modality assessments are limited in their scope. By assessing a single elementary somatosensory modality like touch, an impairment was found in only ~25–40% of stroke survivors, whilst a multimodal testing of elementary sensory modalities revealed dysfunction in ~60% of cases [2, 3]. However, good agreements between different body areas were found within each modality, indicating redundancy of testing between adjacent body regions [2]. The highest sensitivities for sensory impairments after stroke were found by testing discriminatory sensations, such as stereognosis, texture discrimination, position sense, and two-point discrimination. By such testing, impairments were found in 85–89% of stroke survivors [2, 3]. Many studies have described sensory functions using largely subjective scales such as 'absent' versus 'impaired' versus 'normal', thereby restricting interpretability and comparability between studies. New measures have been developed for improved standardized clinical somatosensory testing. The two most frequently used test batteries comprise the Nottingham Sensory Assessment (NSA) [25, 26] and the Rivermead Assessment of Somatosensory Performance (RASP) [26]. Both tests aim to identify sensory deficits after stroke and to monitor their recovery from stroke. The NSA employs eight quantifiable

subtests that can be used in a clinical setting without additional instruments. However, inter-rater reliability is relatively poor even in the revised NSA [25]. There are attempts to further modify the NSA for a better inter-rater reliability [27]. In contrast, the RASP has good inter-rater reliability, but requires additional tests that are not common in clinical practice [26].

Therapy and Prognosis

The main complaint of stroke survivors is loss of somatosensory function. Most patients undergo rehabilitation to regain and relearn lost skills. In the past, rehabilitation training has focused mainly on motor recovery, whereas somatosensory recovery has received less attention. This is probably due to the assumption that loss of sensation is less important for motor recovery. Recent studies, however, have shown that impaired sensory function is associated with the quality of upper limb movement, force control, manipulation of fine-graded objects, and sensory ataxia [4, 23]. The resulting sum of impairments predict poor functional outcome after stroke, including independence in activities of daily life, and even mortality [4, 5]. These findings have increased interest in underlying mechanisms of somatosensory recovery after stroke. It has long been recognized that sensory function following stroke improves during typical rehabilitation training without specific sensory training [2, 28]. Thus, multiple studies were performed to investigate the effectiveness of specialized sensory rehabilitation training [29–32]. In general, these interventions used sensory discrimination tasks [1, 30, 33] and sensory stimulation approaches involving tactile [29], electrical [32], thermal [31], and magnetic stimuli [34]. There is emerging evidence that specialized sensory interventions can result in increased recovery of somatosensory function as well as an improvement of other impairments such as motor function [for review, see 35].

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Headache

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Abstract

Headache can be a symptom of vast pathologies, and common secondary headache including head or neck trauma, cranial or cervical vascular disorder, non-vascular intracranial disorders headache related to a substance or its withdrawals, infection, disorders of homeostasis, disorders of cranium or facial mouth or cranial disorders, and headache attributable to psychiatric. Stroke-related headache has been reported between 7 and 65% and headache is also the most frequent symptom of cerebral venous thrombosis, which is present in nearly 90% of patients.

Headache can be a symptom of vast pathologies, and common secondary headache including head or neck trauma, cranial or cervical intravascular disorder, non-vascular intracranial disorders headache related to a substance or its withdrawals, infection, disorders of homeostasis, disorders of cranium or facial mouth or cranial disorders, and headache attributable to psychiatric [1]. The reported frequency of stroke-related headache varies from 7 and 65% and can occur in ischemic stroke, in transient ischemic attack, and in non-traumatic intracranial hemorrhage, including intracerebral and subarachnoid hemorrhage [2]. Headache is also the most frequent symptom of cerebral venous thrombosis, which is present in nearly 90% of the cases [3].

Acute Ischemic Cerebrovascular Disease

Transient Ischemic Attack (TIA)

The International Classification of Headache Disorders (ICHD) [1] requires the onset of a new type of headache which develops simultaneously with onset of focal deficit. Two other points of the criteria include focal neurological deficit of ischemic origin lasting <24 h and headache resolves within 24 h. However, it is likely that an update of the criteria will be introduced according to the new definition of TIA [4] in the third edition of the ICHD [5]. The headache is more common with basilar than carotid territory TIA, and it is very rarely a prominent symptom of TIA. The differential diagnosis between TIA with headache and an attack of migraine with aura may be particularly challenging [1]. Fisher reported that [6] 7 of 20 patients with vertebrobasilar ischemic attacks experienced headache, usually occipital or occipitalfrontal in distribution. The headache that accompanied TIA was described in 6 patients who subsequently developed a complete internal occlusion. The pain was mild, usually frontal, and sometimes radiating to the occiput and lasted only for the duration of the neurologic deficit. The author also questioned 58 patients with transient monocular blindness (amaurosis fugax) but none felt pain or discomfort with the attack. Grindal and Toole [6, 7] reviewed the case histories of 240 patients with TIA

and selected 58 who had a definite, recorded history of headache. The headache was a prominent symptom in 25% of patients and was the presenting complaint in nearly one third. Of 33 patients with carotid insufficiency, the headache was not localized or generalized in 13 patients and mainly frontal or retro-orbital in 19 patients. Headache in vertebrobasilar insufficiency was a constant feature in the majority of patients with recurrent vertebrobasilar insufficiency and affected the occipital or neck in 15 of 23 cases. Tentschert et al. [8] prospectively studied 2,196 patients with the diagnosis of acute ischemic stroke or TIA. Of the patients with acute ischemic stroke, 27% had headache at stroke onset, and that this was bilateral in the majority of the patients (61%). The study confirmed previous studies which found an association of headache at stroke onset with younger age patients and/or those with a history of migraine. The authors suggested a careful evaluation of young patients with a focal neurological deficit and a history of migraine to avoid the misclassification as 'complicated migraine'. In a recent study by Amort et al. [9], 303 patients were prospectively studied with suspicion of TIA. In summary, about 1 out of 5 patients had TIA mimics and epileptics (43.7%), and migraine attacks (23.6%) were the most common diagnoses among this group; paresis suggested TIA; memory loss, headache and blurred vision were significantly more frequent in patients with TIA mimics.

Acute Ischemic Stroke

The ICHD [1] requires the onset of a new type of headache that develops simultaneously or in very close temporal relation to signs or other evidence of ischemic stroke. Ischemic stroke can cause a migraine syndrome in patients who previously did not have a history of migraine, or can precipitate a migraine attack in patients who are prone to migraine. In addition, patients who have migraine after stroke might continue to experience recurrent migraine attacks. Headaches are more common after major strokes and significantly more frequent in patients with vertebrobasilar territory ischemia than those in the anterior circulation, probably because vessels in the posterior circulation are more densely innerved by nociceptive afferents than those in the anterior circulation. Most aspects of onset headache are debated and there is not a precise definition, though this type of headache might be an indication of the initial vascular occlusion and resultant ischemia [10].

Cervical Artery Dissection

Headache is reported by 60–95% of patients with carotid artery dissections an in about 70% of patients with vertebral artery dissections. Although headaches most commonly have a gradual onset, 20% of patients present with thunderclap onset [11]. According to the ICHD [1], headaches secondary to cervical artery dissection must be ipsilateral to the dissected artery. Headaches due to carotid artery dissection most commonly involve the jaw, face, ears, periorbital, and frontal or temporal region. Headaches due to vertebral artery dissection are commonly located in the occipital-nuchal region. Neck pain is present in 50% of patients with vertebra-artery dissections and 25% of patients with carotid-artery dissection. Associated neurological symptoms and signs include amaurosis fugax Horner's syndrome, pulsatile tinnitus, dysgeusia, diplopia, or other stroke manifestations [11]. In a recent case series of patients with spontaneous cervical artery dissection, pain was the only symptom in 20 out of 245 (8%), and in those particular cases, 12 had vertebral artery dissection, 3 had internal carotid dissection and 5 had multiple dissections. The headache was mainly throbbing in quality and the pain to the neck was mainly constrictive in quality [12].

Intracranial Hemorrhage

Subarachnoid Hemorrhage

The ICHD [1] requires severe headache of sudden onset that develops simultaneously with hemorrhage. The headache is the most common symptom of subarachnoid hemorrhage [11], and

typically the presentation is sudden and severe pain with nausea, vomiting, neck pain, photophobia, and loss of consciousness [2]. The sudden onset of the pain is the most characteristic feature, in fact in 3 out of 4 patients the onset is within a split second or a few seconds. The headache is the only symptom in about a third of the patients in general practice. Headache is generally diffuse and often described by patients as the most severe headache they have ever had. However, the crucial feature is the suddenness of onset and not the severity of the pain. The headache usually lasts 1–2 weeks, something longer. How short in duration a headache from subarachnoid headache can be is not known. No single or combined features of the headache exist that distinguish reliably, and at an early stage, between subarachnoid hemorrhage and non-hemorrhagic thunderclap headache [13].

Intracerebral Hemorrhage

The ICHD [1] requires the onset of a new acute type of headache which develops simultaneously with, or in very close temporal relation to intracerebral hemorrhage. The frequency of headache varies from 13% for putaminal hemorrhage to 50% in the case of cerebellum. 55% of patients with intraparenchymal hemorrhage experienced headache, usually unilateral and severe, at onset. In most patients with cerebral hemorrhage, the headache is overshadowed by the rapid onset of a devastating neurologic deficit, drowsiness, or vomiting [6]. One study prospectively studied 124 patients. 61% of the patients had ischemic stroke and 39% had hemorrhagic (not including subarachnoid hemorrhage type). Headache after acute stroke is frequent, starts usually on the first day of stroke, lasts about 3.8 days and is most frequently continuous, pressure-type in nature, more often located in the anterior cranial region and bilateral. Headache is more severe on the first day of stroke, and on the same day association with nausea and vomiting is frequent. Patients with hemorrhagic strokes had more severe headache and that they start more frequently before other neurological signs, whereas headache in ischemic stroke occurs more frequently in association with other focal signs and it is progressive in onset. A previous history of headaches was documented in 71 patients and the headache in acute stroke was a reactivation of previous headache in 38–53% of the patients, with the trend to complain of the same type of headache if the headache was frequent in comparison with those that had sporadic headache [14].

Cerebral Venous Thrombosis (CVT)

The ICHD [1] requires the onset of a new headache which develops in close temporal relation to CVT. Headache, generally indicative of an increase in intracranial pressure, is the most common symptom in patients with CVT and is present in nearly 90% of patients. The pain is typically diffuse and often progresses in severity over days to weeks. A minority of patients may present with thunderclap headache, suggestive of subarachnoid hemorrhage, and migraine-like pain has been described. Isolated headache without focal neurological findings or papilledema occurs in up to 25% of patients with CVT and presents a significant diagnostic challenge. CVT is an important diagnostic consideration in patients with headache and papilledema or diplopia (caused by sixth nerve palsy) even without other neurological focal signs suggestive of idiopathic intracranial hypertension. The superior sagittal sinus is most commonly involved, which may lead to headache, increased intracranial pressure, and papilledema. For lateral sinus thromboses, symptoms related to an underlying condition (middle ear infection) may be noted, including fever and ear discharge. Additionally, pain in the ear or mastoid region and headache are typical. Headache is also a common complaint during the follow-up sessions with CVT patients, occurring in about 50% of cases. In general, however, the headache is primary and not related to CVT [3].

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Eye Movement Abnormalities

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Abstract

Generation and control of eye movements requires the participation of the cortex, basal ganglia, cerebellum and brainstem. The signals of this complex neural network finally converge on the ocular motoneurons of the brainstem. Infarct or hemorrhage at any level of the oculomotor system (though more frequent in the brainstem) may give rise to a broad spectrum of eye movement abnormalities (EMAs). Consequently, neurologists and particularly stroke neurologists are routinely confronted with EMAs, some of which may be overlooked in the acute stroke setting and others that, when recognized, may have a high localizing value. The most complex EMAs are due to midbrain stroke. Horizontal gaze disorders, some of them manifesting unusual patterns, may occur in pontine stroke. Distinct varieties of nystagmus occur in cerebellar and medullary stroke. This review summarizes the most representative EMAs from the supratentorial level to the brainstem.

Eye Movement Abnormalities in the Cerebral Hemispheres and the Basal Ganglia

Transient conjugate eye deviation (CED) toward the side of the lesion (Prévost's sign), whether accompanied by a concomitant ipsilateral head deviation or not, may occur in up to one-third of acute supratentorial infarcts. CED has more often been associated with right-side infarcts (probably because of lateralized representation of spatial attention in the right hemisphere), more severe neurological deficits and large cortical and subcortical infarcts (particularly on the left side) [1]. Ipsilesional CED may also occur, although less frequently, with small right frontal infarcts and right basal ganglia infarcts. Contralateral CED ('wrong-way eyes') may occur in striatocapsular hemorrhages.

Eye Movement Abnormalities in Thalamic Stroke

Eye movement disorders in thalamic infarcts are common. Combined up- and downgaze palsy and selective upgaze palsy can be due to paramedian thalamic-subthalamic infarcts (more often bilateral than unilateral) and to concomitant ischemia of the rostral midbrain. Complete ophthalmoplegia (loss of all extraocular movements with bilateral ptosis), which suggests neuromuscular junction disorders, may also result from bilateral paramedian and midbrain infarcts. Pure downgaze palsy is seen with bilateral paramedian thalamic infarcts.

Bilateral internuclear ophthalmoplegia (INO) with ptosis, pseudo-sixth nerve palsy (thalamic esotropia) and 'vertical one-and-a-half syndrome' (OAAH) may be seen, though rarely, in unilateral

paramedian thalamic infarcts [2]. Impairment of vertical gaze is common, particularly in large hematomas. Posterolateral hematomas may manifest with a horizontal gaze deviation toward the lesion, skew deviation, ipsilateral Horner's syndrome, horizontal gaze palsy, and convergence spasm (peering at the tip of the nose) [3]. A conjugate gaze deviation opposite to the hematoma ('wrong-way eyes') may be noticed in large medial and global hematomas [3].

Eye Movement Abnormalities in Midbrain Stroke

The midbrain houses the vertical gaze centers at the level of the mesodiencephalic junction. It also contains two of the three ocular motoneurons where neural signals of oculomotor circuitry converge. In cases of midbrain stroke, which are not common compared to most brain regions participating in eye movement control, occurrence of eye movement abnormalities (EMAs), sometimes with complex patterns, is frequent either as an isolated manifestation or, more often, with additional clinical features reflecting pure midbrain or extensive brainstem involvement. Combined upgaze and downgaze palsy and dorsal midbrain syndrome (complete or partial) may result from paramedian midbrain infarcts. Selective upward gaze palsies have often been found in unilateral rather than bilateral midbrain infarcts, while selective downgaze palsy requires bilateral infarcts. In some rare cases, vertical gaze paresis is due to discrete hemorrhages at the mesodiencephalic junction. Small single (ipsi- or contralateral) upper paramedian infarcts may manifest with monocular elevation palsy (combined palsy of the elevator muscles – 'double elevator palsy') and vertical OAAH (vertical palsy in one eye, upward or downward palsy in the other). A variety of nystagmus, torsional, see-saw and convergence-retraction movements (the latter considered to have a high localizing value of tectal lesion) may be seen, mostly with unilateral upper-midbrain infarcts [4, 5].

Nuclear third-nerve palsies, occasionally without other signs of brainstem dysfunction, may reveal middle paramedian midbrain infarcts, in particular, as well as rare minute hemorrhages. These palsies essentially present, though not exclusively, as complete ipsilateral oculomotor palsy together with contralateral superior rectus palsy, partial bilateral ptosis and mydriasis. Infarcts in the anterolateral territory of the middle midbrain and small hemorrhages may produce complete or partial fascicular third-nerve palsy. This clinical finding may be isolated (Achard-Levy syndrome) or associated with crossed hemiplegia, ipsilateral or contralateral hemiataxia or abnormal movements. Finally, nuclear or fascicular trochlear involvement is exceptional. Other EMAs occurring in midbrain stroke are summarized in table 1.

Eye Movement Abnormalities in Pontine Stroke

Critical anatomical structures for horizontal-gaze generation reside in the lower pontine tegmentum. Consequently, pontine EMAs (conjugate or disconjugate) are quite common owing to infarcts or hemorrhages involving mainly, but not exclusively, the medial and lateral pontine tegmentum. They may manifest either in isolation or, more often, accompanied by other clinical signs of pontine dysfunction.

Ipsilateral horizontal gaze palsy is frequently observed in ventromedial and lateral pontine infarcts. All saccadic movements of both eyes toward the side of the lesion are impaired, though vergence movements are still possible. Moreover, a contralateral CED and an ipsilateral gaze-evoked nystagmus may occur. In rare cases, complete horizontal gaze paralysis is observed with bilateral paramedian pontine tegmental infarcts. Isolated lateral rectus palsy is an uncommon sign of strategic infarcts or hemorrhages involving the medial tegmentum at the midpontine level. Fascicular sixth nerve palsy is most often

Table 1. Other EMAs in stroke

Thalamic stroke
Bilateral ptosis, vertical gaze paresis and contralateral conjugate horizontal gaze palsy
Isolated ipsilateral ptosis; ipsilateral Horner's syndrome
Convergence retraction nystagmus
Midbrain stroke
Dorsal midbrain syndrome (Parinaud's syndrome)
Slowness of smooth pursuit movements
Pseudoabducens palsy
Prenuclear syndrome of the oculomotor nucleus; crossed vertical gaze paresis
Skew deviation (including with alternating appearance)
Pontine stroke
Primary-position downbeating nystagmus
Paralytic pontine exotropia
Medullary stroke
Ipsilesional head-shaking nystagmus
Upbeat and bowtie nystagmus
Hemi see-saw nystagmus
Popper type of lid nystagmus
Ocular contrapulsion
Perceptual symptoms: floor on ceiling phenomenon, tilt of subjective visual vertical, ocular tilt reaction (head tilt toward the side of lesion, ocular torsion, and skew deviation)

associated with other long tracts or cranial nerve dysfunction. The classic pontine crossed syndromes (Raymond-Cestan, Millard-Gubler or Foville syndromes) due to ischemia or small hemorrhages are seldom seen [4, 5].

The most common disconjugate disorder is INO predominantly owing to infarcts at the ponto-mesencephalic junction or at the rostral pons, both affecting the medial longitudinal fasciculus. Very rarely, the WEBINO syndrome (wall-eyed bilateral INO) may result from bilateral paramedian pontine or midbrain infarcts. The horizontal OAAH is considered specific for ischemic or hemorrhagic pontine tegmentum damage. Classically, paralysis of lateral conjugate eye movements in one direction ('the one') and INO in the other direction ('the half') occurs. Recently, variants of OAAH syndrome with peculiar patterns have been described (eight-and-a-half, fifteen-and-a-half and sixteen-and-a-half syndromes). Finally, ocular bobbing, never in isolation, usually manifests as intermittent downward jerks of the eyes followed by a slow return to the midposition. This is mainly due to large pontine infarcts or large caudal hematomas, in some instances spilling out of the pons and extending to the medulla or midbrain [4, 5].

Eye Movement Abnormalities in Medullary Stroke

Central vestibular pathways and structures mediating the gaze-holding mechanism are located at the level of the medulla oblongata. As in other brainstem structures, EMAs invariably occur with other clinical manifestations of medullary infarcts and hemorrhages (table 1). Nystagmus in the primary position, usually beating away from the lesion, may occur in up to 85% of patients with lateral medullary infarct (LMI) and in around 30% of patients with medial medullary infarct (MMI). Horizontal gaze-evoked nystagmus beating to the opposite side of the lesion is found in LMI, whereas ipsilesional horizontal nystagmus predominates in MMI. Upbeat nystagmus in the primary position, which is even more marked on upward gaze, has been noticed with unilateral or bilateral MMI. Ipsilateral Horner's syndrome has been variably found in 40–90% of LMI and 15% of MMI cases. Skew deviation with the ipsilateral eye down due to damage to the otolith-oculomotor pathways may manifest in both LMI and MMI. Ocular lateropulsion of Barré (a tonic conjugate eye drift toward the side of the infarct) is also common in LMI and resembles supratentorial CED. Ipsilateral horizontal hypermetric saccades and contralateral hypometric saccades characterize LMI. EMAs in hemimedullary infarcts and in the rare medullary hemorrhages are similar to those found in LMI [5].

Eye Movement Abnormalities in Cerebellar Stroke

The oculomotor cerebellum plays a central role in regulating all eye movements, including saccades, pursuit, vergence and vestibulo-ocular responses. Cerebellar infarcts are infrequent (2% of all brain infarcts) and often associated with extensive posterior circulation ischemia, whereas hemorrhages are slightly more common. Nystagmus in distinct patterns, invariably associated with other cerebellar signs, is the most common oculomotor sign in cerebellar infarcts and slightly predominates in patients with PICA infarctions. Downbeat nystagmus in the primary position, and greater on down gaze, is found mainly in PICA infarcts. It is often present with smooth pursuit deficits and impairment of the optokinetic reflex. Periodic alternating nystagmus may be seen in infarcts involving the flocculonodular area. Upbeat nystagmus has rarely been found in SCA infarcts. Finally, a transient upside-down tilt illusion may occur in rare instances when the medial branch of the PICA supplies both the flocculus and the nodulus [4, 5].

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Visual Dysfunctions

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Abstract

Damage at many different locations within the visual system can result in visual deficits, and a knowledge of the anatomy involved makes it possible to understand these deficits. In this chapter, we will review the visual system from basic anatomy to the description of more complex higher visual function.

Anatomy, Physiology and Blood Supply

Visual information travels in separate pathways for each half of the visual field. Light entering from the right hemifield hits the left half of the retina, on the rear surface of each eye. The inputs from each eye are combined at the optic chiasm where they undergo a partial decussation and enter one of the two optic tracts. Most of the fibers in each optic tract then terminate in the lateral geniculate nucleus, which is the thalamic relay nucleus for vision. Geniculate fibers travel through the internal capsule and corona radiate to the primary visual cortex in the banks of the calcarine sulcus. The optic radiation is called the geniculocalcarine tract, reflecting its origin and termination. A retinotopic organization is maintained in the optic radiation. Fibers representing inferior visual fields are superior (parietal), whereas those representing superior visual fields loop farthest out into the temporal lobe. Macular fibers occupy a broad middle area. The visual pathway ends retinotopically in the occipital cortex above and below the calcarine sulcus (primary visual cortex or Brodmann area 17). Inferior visual fields project to the cortex above the calcarine sulcus and superior fields to the cortex below the sulcus. Throughout the pathway from the retina to the cerebral cortex, the number of fibers and areas of representation for the macula are disproportionately large for the macula's actual size reflecting its specialization for high acuity. In the occipital lobe, the striate cortex is surrounded by area 18 which in turn is surrounded by area 19 which are commonly referred to as the visual association cortex and are heavily interconnected with area 17.

The ophthalmic artery, from the internal carotid artery (ICA), provides all blood supply to the eye by branching into multiple short posterior ciliary arteries and the central retinal artery (CRA). The short posterior ciliary arteries provide blood supply to the optic nerve head below its surface. The optic tract is supplied by branches of the anterior choroidal artery (AChA), which originates from the supraclinoid segment of the ICA. Penetrating branches to the optic tract and to the lateral geniculate body originate from AChA. The lateral geniculate body, other than by AChA, is supplied by the lateral posterior choroidal artery, a branch of the posterior cerebral artery (PCA). The origins of the geniculocalcarine

tracts in the retrolenticular portion of the internal capsule are supplied by the AChAs. The temporal and parietal lobe portions of the optic radiations are supplied by branches of the inferior division of the middle cerebral arteries. The portions of the radiations within the posterior temporal lobe and occipital lobe are supplied by PCA branches. Area 17 is supplied by the calcarine artery branches of the PCAs while the visual association cortex is supplied by the cortical branches of the PCA including the anterior and posterior temporal arteries, the parieto-occipital arteries and the calcarine arteries.

Visual Symptoms (Eye)

Transient Monocular Blindness (TMB). Temporary loss of vision in one eye, also known as amaurosis fugax, may be considered a brief monocular visual obscuration described by the patient as a fog, blur, cloud, mist, and so forth. TMB can be accompanied by scotomas. This vision loss may be quadrantic or total. The duration of visual impairment is usually less than 15 min and rarely exceeds 30 min. Most patients are affected for only 1–5 min. TMB may be caused by transient ischemia in the distribution of the ophthalmic, posterior ciliary arteries, or CRA. Ipsilateral hemispheric symptoms may be present. Vision is usually fully restored after an attack, although in a small number of patients permanent visual loss from retinal infarction is possible. Episodic attacks of fleeting blindness occur as arteriosclerotic plaques progressively narrow the lumen of the ipsilateral ICA, leading to periodic reductions in blood flow, reduced pressure in the ophthalmic artery, transient ocular ischemia, or vascular insufficiency. Often, cholesterol crystal or plugs of platelets (sometimes visible with ophthalmoscope) will detach from an ulcerating plaque in the vessel wall and embolize to distal branches of the carotid and ophthalmic arteries, the CRA, and/or the posterior ciliary arteries, without causing permanent visual loss. For this reason, TMB is regarded as one variety of carotid artery transient ischemic attack, and like other transient ischemic attacks, TMB is a warning of impeding stroke. TMB may be also the presenting symptom of ICA dissection in young or giant-cell arteritis affecting the elderly [1].

Acute Monocular Blindness. Sudden monocular blindness, excluding ophthalmic emergencies (detachment of the macula, acute closed-angle glaucoma, vitreus or macula hemorrhage and factitious visual loss), is the major symptom of an ocular stroke leading to permanent visual loss. Ocular stroke can be due to CRA occlusion, branch retinal artery occlusion or anterior ischemic optic neuropathy (AION) the latter which is the result of infarction of the optic nerve. The principal causes of CRA occlusion are: embolic, occlusion in situ due to thrombosis or hemorrhage into a plaque, arteritis (e.g. giant-cell arteritis, thromboangiitis obliterans and polyarteritis nodosa), vasospasm (e.g. migraine, Raynaud's disease) and hypoperfusion (e.g. high intraocular pressure due to glaucoma, low retinal blood pressure due to a severe ICA stenosis or severe hypotension). At fundus examination, the ischemic retina takes on a white ground-glass appearance, and the normal red color of the choroids showing through at the fovea accentuates the central cherry-red spot of the macula. Within days of the acute event, the retinal opacification, the cherry-red spot, and the nerve fiber-layer striations disappear, and optic atrophy of the optic disk develops. Branch retinal artery occlusion is usually due to an embolus at an arterial bifurcation in a branch of CRA. Symptoms are sudden and can lead to a permanent loss of a sector of the visual field, with retinal infarction corresponding to the vascular territory of the arteriole blocked. The principal causes of AION are: non-arteritic (commonly due to atherosclerosis, collagen vascular disease as systemic lupus erythematosus, severe hypotension, e.g. during surgical procedures, renal hemodialysis, hematological disorders as sickle-cell disease, polycythemia,

thrombocytopenic purpura, leukemia and anemia), an arteritic variety due to giant-cell arteritis, and embolic occlusion, even if rare, of the posterior ciliary arteries as a complication of ipsilateral ICA disease or cardiac surgery. AION is an uncommon complication of ICA occlusive disease. Severe loss of acuity is characteristic of the arteritic form of AION. In arteriosclerotic or embolic AION, partial infarction of the nerve may occur, with a preservation of central vision. The fundus examination reveals swelling of a segment or all of the optic disc which may be indistinguishable from that seen with raised intracranial pressure, pallor of the disc, flame-shaped hemorrhages near the disc and distended veins. Rarely does the ischemic optic neuropathy affect the nerve only proximal to the lamina cribrosa and manifest without disc swelling (posterior ischemic optic neuropathy).

In embolic ocular stroke both ischemic disk changes and an embolus in a branch of CRA may be present. In ocular stroke, an amaurotic pupil (e.g. absence of constriction to light on direct illumination, intact consensual light response, and intact near response) is present when the eye is completely blind. An afferent pupil defect (e.g. impaired direct-light response) is present if some vision is preserved. Rarely, patients with an acute ischemic stroke in the carotid territory also had ipsilateral optic nerve infarction (opticocerebral syndrome). In these cases, hemodynamic infarction was suggested by triggering by a drop in blood pressure, decreased ophthalmic artery flow and perfusion pressure, and cerebral infarction in a watershed area [2].

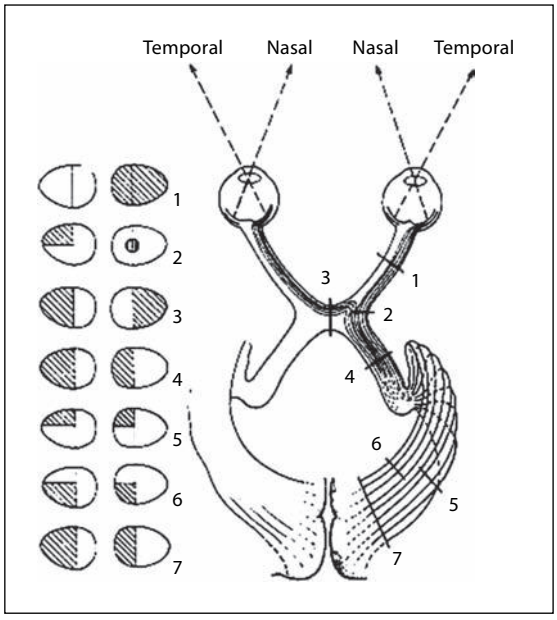

Fig. 1. Topographical diagnosis of visual field defects.

Visual Perceptual Abnormalities (Cerebral)

Visual Field Defects. The nature of a visual defect depends on the location of the lesion (fig.1). A lesion of one optic nerve causes blindness of the eye. Damage in the central region of the optic chiasm, affecting the crossing fibers, causes a heteronymous hemianopia (eyes have non-overlapping field losses; in this case a bitemporal hemianopia). Lateral pressure on one side of the chiasm, affecting the non-crossing fibers on that side, would cause an ipsilateral nasal hemianopia. Double-sided lateral pressure on the chiasm (e.g. bilateral aneurysm of the ICAs), could lead to a binasal hemianopia. Destruction of one optic tract would interrupt all the fibers carrying information from the contralateral visual fields, causing a contralateral homonymous hemianopia. Damage to the optic radiation can cause complete hemianopia but sector deficits are more often the result. For example, a large lesion of the left temporal lobe which represents inferior retinal quadrants would produce a right homonymous superior quadrantanopia. A massive lesion to the visual cortex of one occipital lobe (e.g. after occlusion of one PCA) would result in a contralateral homonymous hemianopia. It has been frequently observed that vision is preserved over much of the fovea. In right homonymous hemianopia, visual loss is often incorrectly referred to the right eye because the right temporal visual field is larger than

the nasal visual field. Lesions of the lower bank of the calcarine fissure are usually accompanied by upper-quadrant visual-field defects while those involving the upper bank of the calcarine fissure are accompanied by lower-quadrant defects [3].

Visual Inattention and Neglect

Hemianopia and inattention can often coexist. In visual neglect, objects in one field are ignored while objects in the other field are not. Neglect usually occurs with large right cerebral lesions involving the temporal and parietal lobes, supplied by the PCAs, or parietal and frontal lobe structures, supplied by the middle cerebral arteries. In patients with PCA territory infarction, neglect is usually limited to visual stimuli, while thalamic, frontal, and anterior parietal lobe lesions usually cause multimodality neglect including visual, auditory and sensory stimuli.

Abnormal 'Positive' Visual Perceptions and Distortions

Visual hallucinations can occur in stroke involving the occipital, temporal and parietal cortices as well as the eye, optic pathways and cerebral peduncle. Diseases of the retina and optic nerves can cause monocular, unformed hallucinations such as sparks, flashes, lights, blobs and spots. Visual hallucination secondary to occipital lesions most commonly consists of elementary (unformed) visual perceptions, sensations of light and colors, simple geometric figures and movements. Posterior temporal lesions, involving the association cortex, result in more complex (formed) visual hallucinations, consisting of physical entities. Lesions in the high midbrain particularly the pars reticolata of the substantia nigra, may give rise to the so-called 'peduncular hallucinosis' of Lhermitte, in which the hallucinations are purely visual, appear natural in form and color, move about as in an animated cartoon, and are usually considered to be unreal, abnormal phenomena [3]. *Palinopsia* refers to visualization of afterimages, that is the image remains for minutes even after the object or the viewer has moved. Most patients have hemianopia and their visual field defects are predominantly left-sided and due to right occipitotemporal lobe infarcts. Visual distortion *(metamorphopsia)* is usually due to bilateral peristriate cortex infarcts but can occur in hemianopic half-field in unilateral lesions.

Other Abnormalities of Visual Perception due to Cortical Involvement

Left Occipital Visual-Related Deficits

Alexia without Agraphia. While writing and spelling are not affected, reading is. This is due to a large left lesion that involves the occipital lobe and the splenium of the corpus callosum. Visual perception of written language performed in the right visual cortex (the left visual cortex is damaged, causing the right hemianopia) is disconnected from the language areas in the left temporal lobe which can be associated to *abnormal color naming. Alexia with agraphia* is when patients cannot read, write or spell after stroke.

For details on *visual agnosia,* see chapter by Acciarresi [pp. 75–78].

Bilateral Posterior Cerebral Hemisphere Lesions

Cortical Blindness. Bilateral lesions of the striate cortex and/or the optic radiations cause bilateral hemianopic defects, often with a sparing visual field portions. Large bilateral lesions can cause cortical blindness even though it is sometimes denied by the patient (Anton's syndrome). In transient or persistent deficits the most frequent causes are emboli of the top of the basilar artery or atherosclerotic occlusive disease of the basilar artery with the involvement of the occipital lobes [4, 5].

For right posterior hemisphere visual-related deficits and lesions of the lower or upper bank of the calcarine fissure, see chapters by Acciarresi [pp. 75–78] and Cereda and Carrera [pp. 128–131].

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Dizziness and Vertigo

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Abstract

Dizziness is a general, non-specific term to indicate a sense of disorientation. Vertigo is a subtype of dizziness and refers to an erroneous perception of self- or object-motion or an unpleasant distortion of static gravitational orientation that is a result of a mismatch between vestibular, visual, and somatosensory systems. Vertigo is among the most common complaints in medicine, affecting approximately 20–30% of the general population. Stroke accounts for 3–7% among all causes of vertigo. The blood perfusion to the inner ear, brainstem, and cerebellum arise from the vertebrobasilar system. Vertigo, nausea, and vomiting, along with nystagmus, represent symptoms of stroke in posterior fossa due to arterial occlusion or rupture of the vertebrobasilar system. However, the spectrum of signs and symptoms as a manifestation of stroke associated with dizziness and vertigo may be variable depending on the affected vascular territories. Stroke or transient ischemic attack should be seriously considered in patients presenting with acute vertigo in the emergency room. Differential diagnosis between vascular vertigo and other causes of vertigo can result in misclassification due to the overlapping of symptoms. Careful medical history, physical examination, neuroimaging and ear, nose, and throat studies may help to distinguish vascular vertigo from other causes.

Definitions and Epidemiology

Dizziness can be classified into four major groups: (1) vertigo, (2) disequilibrium without vertigo, (3) presyncope, and (4) psychophysiologic dizziness. Therefore, vertigo is a subtype of dizziness and refers to an erroneous perception of self- or object-motion or an unpleasant distortion of static gravitational orientation that is a result of a mismatch between the vestibular, visual, and somatosensory systems. Dizziness and vertigo are among the most common complaints in medicine, especially for primary care and family medicine physicians, neurologists, and otolaryngologists. They affect approximately 20 to 30% of the general population [1]. Dizziness and vertigo may be of peripheral origin, including benign paroxysmal positional vertigo (8%), Ménière's disease (5–11%), vestibular neuritis (1.8–4%), or of central origin, including migraine-associated dizziness, postconcussion syndromes, neurodegenerative disorders (i.e. multiple sclerosis, acoustic neurinoma) or cerebrovascular disease (3–7%) [2]. The main causes of vertigo of vascular origin are migraine, transient ischemic attacks (TIAs), and ischemic or hemorrhagic stroke. Vascular diseases account for 3–7% of all causes of vertigo [2].

Blood perfusion to the inner ear, brainstem, and cerebellum arise from the vertebrobasilar system. Therefore, dizziness and vertigo may occur from occlusion or rupture of the vertebrobasilar arteries and their branches. As many as 25% of older patients with risk factors for stroke who present to an emergency department with

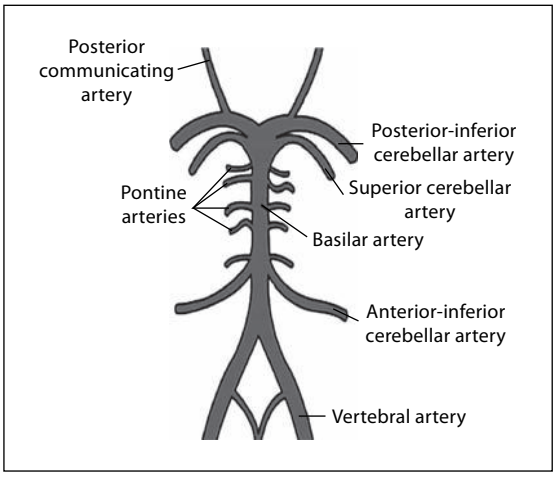

Fig. 1. The vertebrobasilar system.

vertigo have an infarct of the inferior cerebellum. Cerebellar infarction constitutes 1.9–10.5% of all cases in clinicopathologic series of patients with cerebral infarctions [2].

Anatomy of Vertebrobasilar System and Symptoms Associated with Dizziness and Vertigo in Manifestation of Stroke

The vertebrobasilar system includes: the vertebral arteries, the basilar artery and subsequent pontine arteries, the posterior-inferior cerebellar artery (PICA), the anterior-inferior cerebellar artery (AICA), and the superior cerebellar artery (SCA) (fig. 1). The vertebrobasilar system perfuses the medulla, cerebellum, pons, midbrain, thalamus, and occipital cortex. Table 1 presents the brain territories perfused by the PICA, AICA, and SCA with associated clinical features [revised from 1].

Atherosclerosis is the most common cause of posterior circulation ischemia. Other causes of vascular disease leading to posterior circulation ischemia may be lipohyalinosis, aneurysms (most common site being the basilar apex, 60%), arterial dissection (mainly the extracranial vertebral artery), cervical spondylosis, neck trauma, fibromuscular dysplasia, and arteritis [3].

Stroke onset in the brain posterior circulation is sudden and is not predictable by tangible causal factors. The first symptom is usually vertigo, headache, dizziness, confusion, or coma. In fact, most stroke patients who report vertigo have other symptoms related to impairment of the central nervous system. Vertigo, nausea, and vomiting, along with nystagmus, all represent involvement of the vestibular system. Isolated vertigo can be present in just small infarcts of the cerebellum or brainstem. However, the spectrum of signs and symptoms as manifestation of stroke associated with dizziness and vertigo may be variable, depending on the affected vascular territories. Occlusion in PICA may cause the Wallenberger syndrome. Vertigo is its main symptom and is associated frequently with nausea, vomiting, diplopia, limb ataxia, ipsilateral Horner's syndrome, facial anesthesia, contralateral hemianesthesia, dysphagia, dysphonia, ocular tilt reaction, and spontaneous nystagmus. However, medial PICA territory infarction may present isolated vertigo characterized by the absence of nystagmus. It is important to note that acute unilateral peripheral and central vestibular lesions may cause similar symptoms. Due to the anatomical characteristics of the AICA, an occlusion in this artery may cause a combination of peripheral and central syndromes. Typical symptoms associated with this particular occlusion include: sudden unilateral hearing loss and vertigo. Usually these symptoms are also accompanied with ipsilateral facial anesthesia or weakness, lateral gaze palsy, Horner's syndrome, nystagmus, cerebellar dysmetria and contralateral body anesthesia. An occlusion or dissection of the internal auditory artery, which originates from AICA, may cause isolated vertigo without cerebellar signs. Occlusion of SCA is not a frequent cause of central dizziness, however the classic symptoms are vertigo, nausea and vomiting. Other associated symptoms may be ipsilateral limb ataxia, diplopia, contrapulsion of saccade,

Table 1. Perfused brain territories by PICA, AICA, and SCA: Clinical features associated with their occlusion/dissection

Arteries of verterbrobasilar system	Perfused territories	Signs and symptoms after occlusion/dissection
PICA: Posterior-inferior cerebellar artery	Dorsolateral medulla including the inferior part of vestibular nuclear complex, the inferior cerebellar peduncle, and the posterior-inferior cerebellum	Vertigo, nausea, vomiting, diplopia, limb ataxia, ipsilateral Horner's syndrome, facial anesthesia, controlateral hemianesthesia, dysphagia, dysphonia, ocular tilt reaction, spontaneous nystagmus
AICA: Anterior-inferior cerebellar artery	Inner ear, anterolateral regions of the inferior lateral pons, middle cerebral peduncle, and Anterior Inferior Cerebellum including flocculus	Vertigo, sudden unilateral hearing loss, ipsilateral facial anesthesia or weakness, lateral gaze palsy, Horner's syndrome, nystagmus, cerebellar dysmetria, controlateral body anesthesia
SCA: Superior cerebellar artery	Lateral pons, superior cerebeller peduncle, superior cerebellar vermis or hemisphere	Vertigo, nausea, vomiting, ipsilateral limb ataxia, diplopia, contrapulsion of saccade, Horner's syndrome, facial hemianesthesia, controlateral body hemianesthesia

Horner's syndrome, facial hemianesthesia, and contralateral body hemianesthesia.

Another important cause of dizziness and vertigo is the hemorrhage in the brainstem and cerebellum. Vertigo, headache and neck stiffness are the first symptoms suggesting a hemorrhage in the cerebellum. Usually if these symptoms are associated with other neurological signs the prognosis is coma and death. These hemorrhages account for 5–10% of all intracerebral hemorrhages and are most common in hypertensive patients, trauma, patients treated with anticoagulants and in people with vascular malformations, ruptured aneurysms, or bleeding tumors. Patients with hemorrhage in the cerebellum and pons frequently present with flaccid quadriplegia, decerebrating posture, abnormal horizontal eye movements, and coma. Unless surgical decompression is rapidly performed, this condition is often fatal.

Differential Diagnosis and Diagnostic Tests

Stroke should be seriously considered in patients with acute vertigo in the emergency department. Unfortunately, there is a substantial overlap of patients presenting with dizziness for many diseases. Every time that the presentation is atypical for a peripheral vestibular disorder, an ischemic event needs to be considered. For example, isolated vertigo, mimicking labyrinthitis, occurs in partial AICA territory infarcts. To make a differential diagnosis among the possible causes of dizziness and vertigo, it is crucial to take a detailed history and careful description of the symptoms by using words other than 'dizzy'. Dizziness may carry different meanings for different patients such as vertigo, unsteadiness, light-headedness, generalized weakness, presyncope, syncope, or falling. It is crucial to evaluate the presence of other neurological symptoms, such as focal weakness or difficulty to speak. Vision impairment, like mild double vision, is not a discriminatory sign because it may be present in different conditions leading to vertigo. Instead, physical examination could be helpful because peripheral vestibular disorders have characteristic examination features [2]. A patient with unidirectional nystagmus and with no other neurological signs can be diagnosed with vestibular neuritis [2]. Presence of major cardiovascular risk factors should always be considered. It is important to keep in mind that

arterial dissection can occur in the absence of traditional vascular risk factors.

Additional tests may be performed to confirm the diagnosis. The battery of tests includes ear, nose, and throat (ENT) studies, i.e. audiometric and vestibular tests, routine hematology, blood chemistry and coagulation parameters, as well as imaging. Generally both computerized tomography (CT) scans and magnetic resonance imaging (MRI) can document brain infarct, with MRI showing smaller lesions than those seen on CT. MRI is preferred over CT for the smaller infarct and for those in the brainstem, especially in a fluid-attenuated inversion recovery (FLAIR) sequences. Non-invasive vertebral arterial or transcranial Doppler ultrasonography may provide rapid and useful information in the assessment of acute stroke. Echocardiography or angiographic procedures may complete the diagnostic screening by evaluating arterial occlusion in posterior cerebral arteries or presence of aneurysm, vasospasm or dissection. Somatosensory-evoked potentials and brainstem auditory-evoked potentials may provide further information about the etiology and guide treatment decisions [3].

Summarizing, ischemia, hemorrhage, and other vascular disorders can result in various central or peripheral vestibular syndromes with dizziness and vertigo being the main symptoms. Differential diagnosis between peripheral and vascular causes of vertigo is complex and an interdisciplinary approach is needed. Moreover, TIAs should always be a concern in patients presenting with recurrent spontaneous attacks of vertigo, especially if the attacks are frequent and with a short duration between attacks. TIAs may be predictive of a subsequent stroke.

Therapy

The choice of therapy of dizziness and vertigo depends on whether the diagnosis of stroke is confirmed as the cause. Thus, it is important to perform its rapid assessments and identification of prognostic factors of poor outcomes, including infarct size, hemorrhagic transformation, and poor collateral blood flow. Acute thrombolytic treatment with intravenous tissue plasminogen activator should be considered in ischemic stroke within 4.5 h. A careful use of sedatives (benzodiazepines, barbiturates) may be useful. Intravenous fluid and antiemetics (metoclopramide) may be used to reduce vomiting and nausea. Corticosteroid and vestibular suppressants (antihistamines, benzodiazepines, and anticholinergics) can be considered to reduce the symptoms of dizziness and vertigo in selected patients. In patients with hemorrhage and fast decline of consciousness, decompressive surgery of the posterior fossa, with or without removal of hematomas, may be considered [2, 3].

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Auditory Dysfunction

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Abstract

Hearing impairment, although uncommon, may occur in patients with a vertebrobasilar artery occlusion disease. The pathogenesis may be an ischemic lesion involving the auditory pathways in the pons and midbrain, the cochlear nucleus, cochlear nerve or the cochlea. The AICA and IAA are the main arteries that supply the peripheral audiovestibular structures of the inner ear and central audiovestibular pathways of the middle cerebellar peduncle and lateral pons.

In 1943, Adams [1] was the first to describe a neurootologic syndrome associated with AICA occlusion in which bilateral hearing loss was the early initial symptom. Most of the subsequent reports on AICA infarction focused on brainstem and cerebellar symptoms and few studies are available with a systematic evaluation of audiovestibular dysfunction. In patients with an AICA infarction the spectrum of audiovestibular loss is broad. In most of the cases, auditory dysfunction results were associated with vestibular, ocular and other neurological symptoms or signs. Although isolated hearing loss may derive from a selective involvement of cochlear artery (branch of internal auditory artery), this event must be considered extremely rare and other causes, such as viral infection, may be hypothesized.

Anatomy of the Auditory Pathway

The central nervous system receives bilateral acoustic information, consequently an auditory dysfunction produced by a monolateral lesion of the central acoustic pathway is an unusual event, more frequently as a result of a peripheral lesion of the cochlea or cochlear nerve. The acoustic information detected by the receptors of the spiral organ of Corti is transferred to the temporal cortex by a complex polysynaptic pathway, characterized by a bilateral projection.

The axons of the spiral ganglion of Corti constitute the cochlear nerve that penetrates into the internal acoustic meatus together with the facial nerve; the cochlear nerve ends in the bulbar cochlear nucleus (ventral and dorsal). The principal central acoustic pathway arising from the cochlear nucleus is the trapezoidal body, composed of fibers directed to the superior bilateral olivary complex. The axons of the superior olivary complex, together with those directly coming from the cochlear nucleus (homolateral and crossed), converge to compose the lateral lemniscus, directed to the inferior colliculus; from the inferior colliculus the pathway continues to the lateral geniculate and from here to the ispilateral auditory primary cortex [2].

Cochlear Vascularization

The cochlea, vestibule and cochlear nerve are supplied by the internal auditory artery (or labyrinthine artery). The IAA is characterized by a considerable variability including the origin, length, caliber and number; usually it arises from the anterior inferior cerebellar artery (50% of cases) and other anatomic variants directly originate from the basilar artery and from the vertebral artery [3].

The IAA penetrates into the internal acoustic meatus together with the cochlear nerve and facial nerve; at this point it usually gives off the first branch: the subarcuate artery that supplies the superior semicircular canal; then penetration in the acoustic meatus gives off the vestibular artery that supplies the utricle, the posterior and lateral semicircular canals and posterior part of the saccule. The cochlea is supplied by the common cochlear artery that arises from the internal auditory artery. The common cochlear artery divides into two branches: the first is the vestibulocochlear artery that supplies the posterior semicircular canal, the saccule and proximal part of the basal cochlea, and the second branch is the spinal modiolar artery that supplies the main part of the cochlea. Artery circulation of the inner ear is a terminal system; the anastomoses with artery branches deriving from the bony labyrinth, supplied by the external carotid artery, are negligible [4].

Auditory Dysfunction and Stroke

Auditory dysfunction is uncommon in stroke. A hearing loss of vascular origin was reported in ischemic lesions of the cochlea, cochlear nerve, and cochlear nucleus; bilateral infarctions involving auditory pathways in pons and midbrain can produce a bilateral hearing loss [5, 6]. Audiovestibular loss is well documented in infarctions of the anterior inferior cerebellar artery, usually in association with signs of brainstem and cerebellar involvement [7].

An occlusion of IAA is hypothesized as a possible cause of sudden sensorineural hearing loss (SSNHL). SSNHL is a common disease with an estimated incidence of 8 per 100,000 persons [8]. Although the frequency is elevated, the pathogenesis remains controversial; other hypothesized causes are viral or bacterial infection, autoimmune disease, acoustic tumors, and inner ear membrane rupture. In support of the vascular hypothesis that considers SSNHL as an early sign of stroke, in a 5-year follow-up study the risk of stroke was 1.6 times greater among SSNHL patients compared to patients admitted to hospital for other diseases [9]. In contrast with this assumption in systematic studies on audiovestibular loss in AICA infarction, isolated deafness has resulted in being an extremely rare event [10].

In 1943, Adams [1] described an AICA infarction syndrome characterized by facial hyperalgesia, facial palsy, crossed sensory loss, Horner syndrome and vertigo, tinnitus, bilateral hearing loss, gait and limb ataxia; these neurootologic symptoms were described as early symptoms. Most reports on AICA infarction have focused on brainstem and cerebellar symptoms, and few studies are available with a systematic evaluation of audiovestibular dysfunction [11–15].

In a study published in 2002, Lee et al. [16] investigated the incidence of deafness associated with AICA infarction and the sites involved. After 2 years of observation, 12 consecutive patients with AICA infarction diagnosed by brain MRI were identified. Each patient completed a standard questionnaire on vestibular symptoms and underwent a neurootologic examination to discriminate the neural and cochlear cause of hearing loss consisting of a pure-tone audiogram, speech discrimination test, and auditory brainstem response (ABR). Hearing loss of cochlear origin was defined by an increasing hearing threshold on PTA, no abnormalities on ABR and normal stapedial reflex threshold. Vestibular function tests were performed by computer electronystagmography. All patients had vertigo accompanied

by nausea and vomiting as the initial symptom and nystagmus on neurological examination, horizontal-rotatory beating away from the side lesion (toward the healthy side), the rotatory component was clockwise in patients with left beating nystagmus and counterclockwise in patients with right beating nystagmus. A sensorineural hearing loss was found in 11 patients (92%). The complete syndrome described by Adams [1] was revealed in only 2 patients, the most frequently associated sign was facial hyperalgesia in 6, facial nerve palsy was present in 3 patients, and crossed sensory loss with Horner's syndrome in 3. Isolated vertigo and hearing loss occurred from 1 day to 2 months before stroke in 4 patients.

On MRI in 92% of cases (11 patients) the site of infarction was localized in the middle cerebellar peduncle and in 1 patient only in the anterior inferior cerebellum. Ten patients reported hearing loss during the vertigo attack, 1 patient did not notice decreased hearing during the attack but PTA showed a mild hearing loss on the side of lesion, and 1 patient had no auditory loss and PTA was normal. The site of the lesion was identified as cochlear in 6 (50%) patients (mild-moderate hearing loss on PTA with normal response to ABR and stapedial reflex threshold) and retrocochlear in 1 patient (mild hearing loss on PTA, absent response to ABR and stapedial reflex threshold); in 4 patients the site of the lesion was unknown (severe or profound hearing loss on PTA, absent response to ABR and stapedial reflex threshold); all tests were normal in 1 patient. The hearing loss gradually improved in 7 patients within a variable time of 1 week to several months.

In a more recent study over 8.5 years the same authors prospectively identified 82 consecutive patients with anterior inferior cerebellar artery territory infarction diagnosed by MRI and defined the spectrum of the audiovestibular dysfunction. All patients underwent a standardized questionnaire and neurootologic evaluation including a caloric test and pure-tone audiogram [10]. An auditory loss of vascular origin was defined as a decline of hearing noted by the patient and a sensory neural hearing loss documented by pure-tone audiogram; a central vestibular dysfunction was defined as an acute prolonged vertigo >24 h associated with a normal response to standardized caloric stimulation and the presence of central ocular motor or vestibular signs on clinical examination (asymmetrical abnormalities of pursuit or optokinetic nystagmus, gaze-evoked bidirectional nystagmus, impaired modulation of the vestibular response using visual input).

Vertigo and vestibular dysfunction (peripheral, central or combined) resulted in being the most frequent symptoms (98%), a vestibular labyrinth infarction was present in 65% of the cases, a cochlear infarction in 63%, a combination of vestibulocochlear infarction in 60%, and an isolated infarction of vestibular or cochlear in less than 5% of the cases. The most common pattern of presentation resulted in a combination of vertigo associated with audiovestibular dysfunction (canal paresis and sensory neural hearing loss), ocular motor dysfunction and other neurological symptoms or signs (58% of the cases), in 27% of these, audiovestibular disturbances were prodromal symptoms; isolated auditory loss was present in only 3 patients.

In conclusion, audiovestibular dysfunction is an important sign in AICA infarction. The AICA is the main artery that supplies the peripheral audiovestibular structures of the inner ear and central audiovestibular pathways of the middle cerebellar peduncle and lateral pons. Although an isolated vertigo or hearing loss may derive from a selective involvement of the vestibular or cochlear artery (internal auditory artery), this event must be considered extremely rare and other causes, such as viral infection, may be hypothesized.

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Seizures

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Abstract

Seizures can be a clinical presentation of acute stroke or complicate the clinical course of patients with stroke. Post-stroke seizures are significantly more common in patients with cortical involvement, severe and large size stroke and those with cortical hemorrhagic transformation of ischemic stroke. The influence of post-stroke seizures on functional outcome is controversial. The differences concerning the pathophysiology of and recurrence risk for early and late seizures suggests the need for a specific management. The choice of the antiepileptic drug will be influenced by the risk of drug interactions and possible side effects, especially in the elderly. Currently there is no evidence to support the use of antiepileptic drugs in patients with stroke in the absence of seizure even in the presence of risk factors for developing seizure.

Seizures can occur at stroke onset or may complicate the clinical course of stroke. Although there are different definitions of seizure post-stroke, most authors identify early seizures (ES) as those occurring 7–14 days after stroke onset while seizures occurring after this time window are defined as late seizures (LS) [1–4]. This distinction underlies possible differences concerning the pathophysiology of and risk factors for ES and LS. ES frequency has been reported in prospective studies between 2 and 6% of stroke [2, 3], while the risk for LS has been found to between 2.4 and 5.4% [5]; about half of these patients will present recurrent seizures leading to post-stroke epilepsy. Simple partial seizures are the most commonly reported and account for about half of the post-stroke seizures while the remaining are equally divided into complex partial spells and generalized clonic-tonics [6]. The incidence of SE post-stroke has a range of 1–10%. Rarely does the SE represent the onset of acute stroke; it is more often non-convulsive with an increased morbidity and mortality [7]. The occurrence of SE post-stroke does not predict epilepsy [8].

Pathophysiology

The etiology of ES after stroke is not completely understood but several mechanisms have been hypothesized: cellular biochemical dysfunction with membrane instability of injured cells; transient excitoxic neurotransmitter release such as glutamate secondary to hypoxia; alteration of energy metabolism; free radical damage transient, and depolarizations of the ischemic penumbra with a resulting electrical irritable tissue [9, 10]. While the epileptogenesis of LS is probably due to the formation of scars, changes of membrane properties and progressive neuronal post-stroke change [5].

Risk Factors

Several studies have sought to identify the factors which predispose to seizures after ischemic and

hemorrhagic stroke. Regarding ischemic stroke risk factors, no significant relationships seem to exist between seizures and hypertension, diabetes mellitus, smoking, hyperlipidemia, ischemic heart disease, atrial fibrillation or previous TIA [2, 3, 10]. Cardioembolic infarction is usually considered an important risk factor for ES [11], however some large studies have not found statistical differences between embolic and thrombotic infarcts and seizure [1, 12]. A higher presence of ES in hemorrhagic stroke has not been confirmed in all studies [13, 14]. Stroke severity and stroke with large cortical involvement are the more often reported predictive factors for ES [1, 2, 14]. ES after stroke onset is possibly the clinical mirror of cortical brain damage. In fact, the cortical irritation may increase excitability and lead to the onset of seizure. The clinical relevance of the cortical involvement for the development of ES has been suggested by a prospective study, based on EEG in acute stroke patients [15]. This study reported a relationship between electrical epileptic activity and cortical lesion. In a prospective study of 368 consecutive patients with a first-ever acute ischemic, the cortical hemorrhagic transformation (HT) of ischemic stroke resulted being an independent clinical factor for developing seizures (OR 6.58; 95% CI 1.95–22.61; p = 0.003) and in all patients except 1, the HT resulted in being cortical [10]. The presence of HT, especially in the cortical region with edema development, could increase the excitability of the cortical ischemic penumbra tissue, which is already suffering. The increased brain excitability in the presence of HT has been supported by a study that has evidenced HT as an independent predictor of status epilepticus in acute ischemic stroke [16].

Outcome

The influence of post-stroke seizures on functional outcome is controversial. Regarding morbidity, the occurrence of ES can increase physical disability [1] while other studies have not confirmed these data [17]. A persistent worsening of stroke sequelae after LS has been reported in a small cohort study where the worsening of the neurologic deficit was associated with longer seizures and related to a direct effect of the seizure on ischemic area [18]. Several studies have reported a higher mortality in patients with post-stroke seizures [1, 3, 19]. Some authors have hypothesized that ES in ischemic stroke patients could worsen the outcome, due to additional metabolic stress in the suffering penumbral area [9, 14]. However, there are no available data suggesting that ischemic damage could be worsened by hyperexcitability and electric activity of cell membranes in necrotic tissue. Additionally, other studies, after accounting for stroke severity, have found that seizure was not a predictor of mortality [2, 10, 14].

Management

Stroke is the most common cause of symptomatic seizures in the elderly [20]. Being so, the occurrence of a seizure in elderly patients should alert the specialist to the possibility of a first or recurrent stroke event. In patients with acute stroke that present a suddenly impaired consciousness, the possibility of non-convulsive status epilepticus should be considered; an electroencephalography study may help to detect the epileptic patterns. In the presence of SE and prolonged ES, antiepileptic treatment should be started immediately, because a prolonged focal motor seizure may cause worsening of the previous motor deficit [18].

Regarding prevention of recurrent seizure, the differences concerning the pathophysiology of and recurrence risk for ES and LS suggest a different management (fig. 1). ES has a low recurrence risk: the choice of starting antiepileptic drugs (AEDs) for prevention of recurrent seizure is influenced by seizure type and risks factors, and the antiepileptic treatment could be stopped a few months after stroke. In patients with LS, the high risk of recurrence [21] necessitates, especially in the presence of cortical or large size lesions, the administration of antiepileptic treatment for at

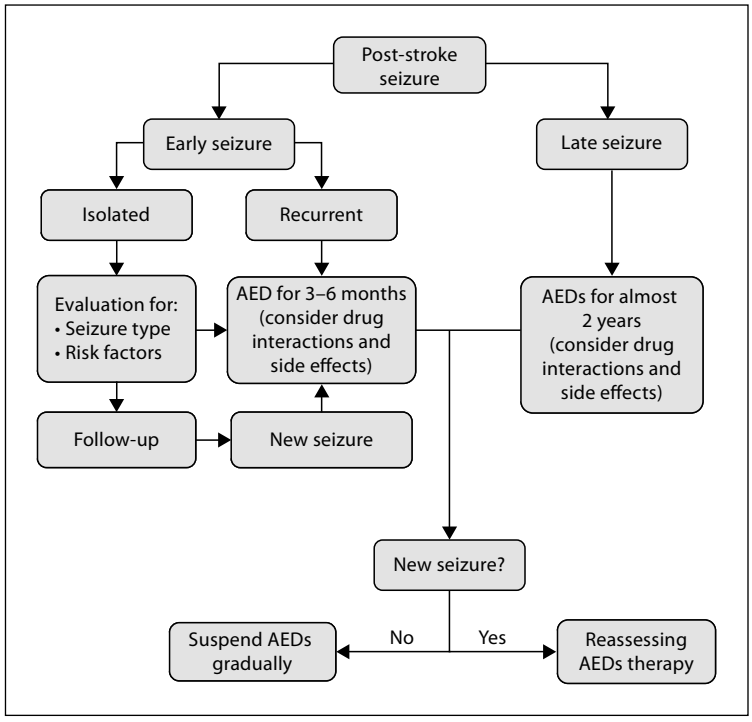

Fig. 1. Management of post-stroke seizures.

least 2 years. The choice of anticonvulsive therapy will be influenced by the risk of drug interactions and possible side effects, especially in the elderly. At same time, phenytoin, phenobarbital and benzodiazepines have been reported to delay stroke outcome. The administration of new AEDs should be reserved for patients with contraindications to classic AEDs [22]. Currently, there is no evidence to support the use of AEDs in patients with stroke in the absence of seizure, even in presence of risk factors for developing seizure [23].

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Impaired Consciousness

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Abstract

Coma and other states of impaired consciousness are common in stroke patients. Sudden disturbance of consciousness can be the predominant clinical syndrome in the brainstem stroke, particularly in the case of basilar artery occlusion. Clinicians need to thoroughly investigate for the presence of stroke in patients with sudden disturbance of consciousness.

Physiology and Pathophysiology of Consciousness

Consciousness is defined as the ability to relate both to oneself and to one's environment and is divided into two main components: *arousal* (wakefulness, alertness or vigilance) and *awareness* (awareness of the environment and of the self) [1]. Both aspects of consciousness depend on the integrity of the ascending reticular activating system (ARAS) which extends from the medulla to the thalamic neurons [2]. Coma is a state of continuous 'eyes-closed' unconsciousness, in the absence of a sleep-wake cycle [3]. Disorders of arousal are expressions of ARAS dysfunction that can be caused directly by a brainstem lesion or indirectly by damage to the cerebral hemisphere [2]. Therefore, extensive bilateral damage of the hemisphere function is required to produce coma; in fact, a unilateral hemisphere lesion will not result in coma unless there is secondary brainstem compression, caused by herniation which in turn compromises the ARAS, by vertical or horizontal displacement of the brain. In patients with thalamic-subthalamic lesions, even if bilateral, coma is often transient, frequently evolving into a sleep-like somnolence with apathy and akinetic mutism [2]. Lesions below the level of the pons do not normally result in coma [4].

Impaired Consciousness

Coma and other states of impaired consciousness are common in stroke patients. In a large study of patients with 'medical coma', cerebrovascular disease accounted for 50%, hypoxic ischemic injury for 20%, and various metabolic and infective encephalopathies for 30% of the cases [5].

Analysis of alterations in consciousness pattern among stroke patients is of great clinical interest. The degrees of impairment of consciousness can help to determine the locations of infarctions: severe impairment of consciousness suggests the presence of large hemispheric or bilateral brainstem lesions. Moreover, the level of consciousness is a good predictor of outcome in the presence of stroke. In fact, impaired consciousness has been reported to be a significant predictor of mortality in several studies [6–8]. Finally, patients with impaired consciousness need different monitoring and therapeutic strategies: an accurate assessment of the arousal and awareness of consciousness in

stroke patients is of great importance for their correct management.

Transient Loss of Consciousness and Stroke

Transient loss of consciousness (T-LOC) is a common medical problem accounting for approximately 3% of emergency room visits [9]. Syncope is the most common cause of T-LOC. Cerebral ischemia and transient ischemic attacks are uncommon causes of syncope. Cardioembolic stroke is associated with an enhanced risk of syncope at onset [10]. Some reports have found that severe bilateral carotid artery stenosis and carotid occlusive disease to be causes of syncope, in the absence of clinical or electroencephalographic activities. Carotid stenosis and carotid hypersensitivity can lead to cerebral hypoperfusion because of inappropriate development of collateral circulation [11].

T-LOC, although rarely, can be caused by vertebrobasilar transient ischemia. A recent retrospective study has found that attacks account for up to 8% of cases of T-LOC [12]. These patients tended to be elderly males with ischemic heart disease reporting symptoms of vertebrobasilar insufficiency such as vertigo, ataxia, or paresthesia [13].

Coma and Stroke

The percentage of coma ranges from 5 to 18% following ischemic stroke while it is 31–55% following intracerebral hemorrhage [14]. In patients with hemispheric infarction, coma appears after 2–4 days of progressive clouding of consciousness, due to infarct swelling and secondary midline shift and displacement of intact brain. Cerebellar infarction needs to be constantly monitored due to its unpredictable clinical course. In brainstem compression, a direct mass effect as well as evolution of obstructive hydrocephalus due to compression of the fourth ventricle are the two main causes of deteriorating cerebellar stroke [15]. A sudden disturbance of consciousness can be the predominant clinical syndrome in brainstem stroke, particularly basilar artery occlusion, especially when the etiology is embolism.

On admission, the percentage of comatose patients with basilar occlusion ranges from 30 to 40%. In case of basilar embolism, Schwarz et al. [16] have found that 33% of patients had an acute, complete loss of consciousness at onset. In patients with basilar artery occlusion presenting with coma, the basilar artery was occluded in most of the cases at its rostral end; thus it would be appear that the adequacy of the circulation in the penetranting pontine branches of the basilar artery may be the critical factor determining severity symptoms. The critical area for consciousness in humans is the paramedian pontine tegmental gray matter extending continuously from the posterior hypothalamic reticular formation rostrally to the pontine tegmentum caudally. This area is supplied by the penetrating branches of the basilar artery and the thalamoperforating branches of the posterior communicating and posterior cerebral arteries [17]. Physicians must always consider the possibility of brainstem stroke in coma patients as basilar artery embolism rarely has prodromal symptoms.

Coma-Like Conditions and Stroke

There are two conditions where the patients present a separate involvement of ARAS and motor pathways: preserved spared ARAS and tetraplegia (locked-in syndrome); preserved motor pathways and the involvement of the ARAS (akinetic mutism) [2].

Locked-in syndrome is characterized by quadriplegia and anarthria with preserved consciousness and vertical eye movement. Anarthria is due to bilateral facio-glossopharyngo-laryngeal paralysis, which also causes dysphagia, thereby limiting the use of facial expression. Although medial and lateral gaze palsies are typical, upper eyelid control is usually retained as well as vertical eye movement, due to mid-brain tectum sparing, which allows for communication [18]. Locked-in syndrome is

associated with acute bilateral pontine stroke for the occlusion of paramedian arteries and perforators of short circumferential arteries (terminal arteries) sparing the territories of long circumferential arteries and reticular formation (fig. 1).

Due to recent advances in medical care, life expectancy and quality of life have increased greatly.

Akinetic mutism is characterized by a lack of spontaneous movements with little or no vocalization in subjects with intact corticospinal pathways. This was first described in a patient with diencephalic damage. Different forms of akinetic mutism have been described [2], namely: (1) large frontal stroke: additional clinical features include urinary incontinence, normal wakefulness and grasping; (2) bilateral paramedian thalamic artery infarction and thalamomesencephalic strokes: additional clinical features include disturbances of vertical eye movements and hypersomnia; (3) bilateral caudate stroke (abulia minor), and (4) bilateral deep lesions of the frontal white matter or of the basal ganglia (especially globus pallidus). Additional clinical features include extreme apathy and indifference without suffering or depression.

Vegetative state is a coma-like condition where patients are awake but are unaware of themselves and their environment; limb movement is without purposeful manner and preserved autonomic function [4]. A vegetative state is usually caused by large and bilateral lesions of the cerebral hemispheres with sparing of the brainstem.

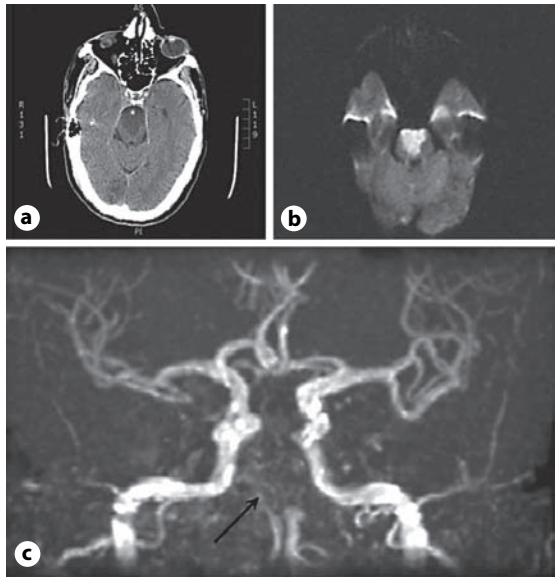

Fig. 1. **a** CT scan showing a hypodense area within the pons and hyperdensity of the basilar artery. **b** Diffusion-weighted MRI showing recent infarction of the pons. **c** Angio-MRI showing occlusion at the origin of the basilar artery (arrow).

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Sleep Changes

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Abstract

Sleep difficulties are frequent among stroke patients. Sleep and stroke can be related in several ways: sleep disturbances such as insomnia and hypersomnia can be triggered by stroke; sleep-related breathing disorders such as snoring and sleep apnea are well-recognized risk factors of ischemic stroke; finally, sleep disorders can be aggravated by stroke. Sleep problems are associated with all stroke types and worsened stroke outcome. Post-stroke sleep disturbances may be a direct consequence of lesions caused by stroke or may be secondary to pain, disability and mood disorders due to stroke. Clinicians need to thoroughly investigate for the presence of sleep disorders in rehabilitating stroke patients.

Stroke is the leading cause of long-term disability. Post-stroke manifestations such as aphasia and paralysis can be devastating and often physicians do not take into consideration sleep disorders. Yet, several studies have reported a greater prevalence of sleep disturbances in patients with stroke compared to the general population: more than 50% of patients with stroke have sleep breathing disorders [1, 2], while 20–40% of stroke patients have sleep-wake disturbances [3, 4]. These disorders are sometimes transitory but in some patients they are chronic and thus having a highly negative impact on stroke outcome [5].

Sleep disorders and stroke can be related in several ways: sleep-related breathing disorders such as snoring and sleep apnea are recognized independent risk factors for ischemic stroke ischemic; sleep disorders such as insomnia and hypersomnia can be triggered by stroke; finally, sleep disorders can be aggravated by acute stroke.

Sleep Disorders in Stroke Patients

Polysomnography studies carried out on patients with stroke have evidenced alterations in sleep architecture. Fragmentation of sleep, reduction in total sleep time and sleep efficiency, increased sleep latency and a decrease in both REM and NREM sleep have been reported more often in stroke patients [6]. The anatomical structures involved in the control of sleep are for the most part localized in the brainstem: the arousal level is maintained by the reticular activating system which extends from the medulla to the thalamic neurons; the cycles during sleep are regulated by pontine nuclei. So, stroke with brainstem vascular lesions are more often associated with sleep disorders. However, sleep pathophysiology is complex and any attempt to correlate sites of vascular lesions to a specific sleep disorder is not always reliable. Moreover, concurrent pain, disability and mood disorders following stroke could contribute to sleep disturbances.

Insomnia [inability to obtain an adequate amount or quality of sleep]: Insomnia is frequently reported in patients with acute stroke. In a study among 277 patients with stroke, 56.7% of these reported insomnia [3]; insomnia in stroke patients has been reported most often with subcortical, thalamic and pontine lesions [1, 2]. Anxiety, dementia, disability and the use of psychotropic drugs have resulted in being independent risk factors for insomnia in stroke patients [3]. Insomnia has a significant impact on the patient's performance: excessive daytime sleepiness, fatigue, memory and attention problems often leading to stress and depression. *Treatment*: sleep hygiene is first-line therapy: mobility and exposure to daylight and silent sleeping quarters can reduce insomnia, especially in the first days after stroke when patients often present an inversion of the sleep-wake rhythm. With regard to therapy, zolpidem or short half-life benzodiazepines should be administered with prudence. In patients with depression, a sedative antidepressant is a good therapeutic option.

Hypersomnia [excessive daytime sleepiness]: Hypersomnia is common in stroke patients. Stroke lesions that involve the arousal level system are more likely to induce hypersomnia. Paramedian thalamic stroke, especially if bilateral, causes severe hypersomnia which is often associated with severe cognitive impairment [7]. Hypersomnia has been correlated also with large cortical strokes. Hypersomnia may persist for months with an important negatively impact on stroke outcome. *Treatment*: stimulating antidepressants or modafinil can improve the disturbance.

Sleep-related movements disorders [restless legs syndrome (RLS): unpleasant feelings in the legs associated with a need to move that occurs at rest or at night; periodic limb movements (PLM): episodes of repetitive limb movements that occur during sleep]: Recent studies have found a greater prevalence of RLS and PLM in patients with ischemic stroke compared to the general population [8, 9] suggesting that these sleep movement disorders may be a direct consequence of stroke. A study among 137 patients with stroke has reported 12% of patients with RLS. The basal ganglia and/or corona radiata (30%), pontine (22%) and thalamic infarct (14%) were the lesions more related to stroke while RLS was very rarely associated with cortical lesions [10]. RLS and PLM often coexist. *Treatment of RLS:* dopamine agonists are first-line therapies.

REM behavior disorders (RBD) [parasomnia characterized by loss of normal voluntary muscle atonia during REM sleep associated with complex motor behavior while dreaming]: More frequently associated with neurodegenerative disorders, RBD has been documented in stroke patients especially with pontine lesions [11]. *Treatment*: clonazepam in the evening.

Sleep breathing disorders [obstructive sleep apnea (OSA): apnea during sleep due to airway blockage caused by the relaxation of the muscles in the airway; Cheyne-Stokes respiration (CSR): form of periodic breathing in which central apneas alternate with hyperpneas that have a waxing-waning pattern of tidal volume]: Sleep breathing disorders (SBD) are frequent in stroke patients, often improve after the acute stroke phase and are associated with an adverse outcome [12]. OSA and RCS are the most common form of SDB and often coexist. OSA is a well-recognized risk factor for ischemic stroke: recurrent hypoxias, intrathoracic pressure changes, cardiac arrhythmias and cerebral blood flow fluctuations are considered as principal pathophysiological mechanisms for stroke [13]. OSA can also occur as a direct consequence of stroke: medullary lesions are the most commonly reported; moreover, a relaxation of the muscles in the airways in the acute stroke can cause or aggravate a preexisting OSA. CSR during sleep has been frequently reported in brainstem or hemispheric stroke. Older age, stroke severity/extension, and lower left ventricular function have been reported to be risk factors for CSR [14]. Classically the majority of CSRs improve after a few days following stroke. *Treatment:* OSA: continuous positive airway pressure is the principal treatment. CSR: in

a severe and persistent form, positional therapy, low-flow oxygen or when OSA is present, positive airway pressure can be used [2].

Conclusion

Sleeping disorders are common in stroke patients. Sleep problems are associated with all stroke types and the increasing of sleep disturbance is associated with an important negatively impact on stroke outcome. Clinicians need to always thoroughly investigate for the presence of sleep disorders in rehabilitating stroke patients.

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Aphasia and Other Language Disorders

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Abstract

Aphasia refers to a disorder of language processing caused by a dysfunction in specific brain regions. It is common after stroke and associated with relevant disability and higher mortality. Evaluation of language function (spontaneous speech, auditory comprehension, naming, repetition, reading and writing), allows classification of aphasia. Most patients present some degree of recovery. Speech and language therapy is an effective treatment for aphasia following stroke. Other approaches, e.g. pharmacotheraphy, transcranial magnetic stimulation, are being investigated. Other language disorders are mentioned.

Definition

Aphasia refers to a disorder of language processing caused by a dysfunction in specific brain regions that provoke various combinations of impairment in the ability to spontaneously produce, understand or repeat speech, in addition to defects in the ability to read and write. It consists of a breakdown in the two-way translation process that establishes a correspondence between thoughts and language [1].

Epidemiology

Together with traumatic brain injury and degenerative dementias (e.g. Alzheimer disease), stroke is a major cause of aphasia. The percentage of aphasia in acute stroke patients ranges from 14 to 38% [2, 3] and this difference may be explained by different methods of evaluation (i.e. sophisticated batteries [2] vs. basic bedside evaluation [3]), time of testing after stroke onset (vascular aphasia evolves rapidly during the first hours) and diverse methods for classification. In a large recent study, aphasia was detected in 26% of patients with first-ever stroke [3]. One study that assessed patients within the first week showed that global aphasia was the most common aphasia subtype in the acute phase (32%), followed by Wernicke's (15%) and Broca's aphasia (12%) [2]. Aphasia is associated with relevant disability after stroke and higher mortality. Although it was suggested that aphasia was more severe in women than in men, this was not confirmed in recent studies. Moreover, aphasia was not more frequent in older patients than in younger ones in the acute stroke phase. However, the relationship between age and aphasia and its subtypes may depend on time of evaluation after stroke. Studies performed in the non-acute phase showed a predominance of fluent aphasia in older patients.

Evaluation

The first goal of the examination is to establish whether a patient has a language disturbance or not, and, if present, try to identify the aphasic disorder and syndrome. Although evident deficits may

Table 1. Principal aphasic syndromes [1, 4]

Type	Fluency	Comprehension	Repetition	Naming	Reading	Writing	Associated signs
Broca's	–	+	–	–	–	–	right arm weakness, apraxia of speech
Global	–	–	–	–	–	–	hemiplegia, hemihypoesthesia, hemianopia
TMA	–	+	+	–	+/–	–	variable
Apraxia of speech	–	+	–	–	–	+	none
MTA	–	–	+	–	–	–	variable
Wernicke's	+	–	–	–	–	–	quandrantanopia, hemihypoesthesia
Conduction	+	+	–	+/–	+	+	usually none
Anomic	+	+	+	–	+	–	variable
TSA	+	–	+	–	–	–	variable

TMA = Transcortical motor aphasia; MTA = mixed transcortical aphasia; TSA = transcortical sensory aphasia.

de disclosed during history taking, formal assessment is often required. Moreover, non-linguistic items of the neurological examination (e.g. motor, sensitive) may help in the classification of the stroke syndrome (table 1). Knowledge of the patient's handedness is fundamental. Exceptionally, right-handed individuals develop aphasia as a result of right cerebral lesions ('crossed aphasia').

Six items of the language function should be tested, namely spontaneous speech, auditory comprehension, naming, repetition, reading and writing. This can be done by bedside examination, but for detailed evaluation, several batteries (e.g. Boston Diagnostic Aphasia Examination and Montreal-Toulouse battery) are available.

Classifications

The most commonly used classifications in clinical practice are outlined in table 1 [4].

Broca's Aphasia. It refers to a primary deficit in language output with relative preservation of comprehension. The spontaneous speech is non-fluent: slow and labored with long pauses, reduced phrase length, impaired melody and agrammatism (failure to follow grammatical rules and improper use of conjunctions, prepositions and auxiliary verbs). Patients may present recurring utterance. Although comprehension for conversations and grammatically simple sentences is preserved, patients may have difficulties with more complex sentence structures, such as passive voice. Patients have more troubles to name verbs than nouns. Broca's aphasia is caused by lesions in the territory of the anterior division of the left middle cerebral artery (MCA) involving the Broca's area (the inferior frontal gyrus, BA 44 and 45) and the surrounding frontal areas, underlying white matter and subjacent basal ganglia. In patients with lesions restricted to Broca's area, the only deficit may be impaired motor planning and programming of motor speech. This disorder is called apraxia of speech, 'Broca area aphasia', mini-Broca or baby Broca. Even more restricted damage to Broca's area may produce a closely related syndrome called 'aphemia' which is characterized by disturbance of speech without a true language defect [1].

Wernicke's Aphasia. It is characterized by poor comprehension of words, sentences or

conversation and fluent but meaningless spontaneous speech and repetition. Jargons comprised of either real words or neologisms are common as well as semantic paraphasias (wrong words related by meaning). Patients may be unaware of the disturbance (anosognosia) and develop agitation and paranoid ideation. The condition is usually caused by a lesion in the posterior division of the MCA involving the Wernicke's area (posterior, superior temporal gyrus, most of BA 22).

Global Aphasia. This syndrome is characterized by an almost complete loss of the ability to formulate speech or comprehend language, combining the deficits of Broca's and Wernicke's aphasia. Spontaneous speech, naming and repetition may be limited to a single preservative word or non-word utterance. In a significant proportion of patients, comprehension recovers well, changing from global to Broca's aphasia *(Syndromenwandeln)*. The damage usually involves most of MCA territory. More rarely the damage is caused by two lesions, one frontal and other parietotemporal, sparing parts of the sensory and motor cortex. These patients may have transient or no hemiplegia ('global aphasia without hemiplegia').

Conduction Aphasia. It refers to severely impaired repetition with relatively fluent, accurate spontaneous speech with phonemic paraphasias (responses phonetically related to the target word). Some patients may struggle to approximate the target phonemes *(conduits d'approche)*. The vascular lesion often involves a terminal branch of the MCA. It was proposed that conduction aphasia represented one of the disconnection syndromes, due to disruption of the arcuate fasciculus which connects the anterior and posterior perisylvian language areas [5]. However, many reported patients had lesions in the supramarginal gyrus and deep parietal white matter and patients with lesions of the arcuate fasciculus did not consistently present this subtype of aphasia.

Transcortical Aphasias. These syndromes are characterized by preserved repetition. The motor variant has many features of the Broca's aphasia but with normal repetition. There is involvement of the left frontal cortices above and in front of the Broca area caused by occlusion of the anterior cerebral artery (ACA) or by borderzone infarcts between the territory of the MCA and ACA. The sensory variant consists of fluent, semantic jargon, poor comprehension and good repetition. It is attributed to posterior lesions around the Wernicke area caused by infarcts in the territory of the posterior cerebral artery (PCA), posterior branches of the MCA or borderzone infarcts between the MCA and PCA. It has also been described after thalamic lesions. The mixed type, also known as 'isolation syndrome', has features of both motor and sensory transcortical aphasias. The lesions tend to surround the MCA territory, often in watershed areas, isolating the language areas.

Anomic Aphasia. This is the mildest form of aphasic syndromes, with fluent speech, preserved comprehension but with naming and word finding difficulty. This syndrome is not specific of a cerebral region, but may be present after a wide distribution of infarcts.

Subcortical Aphasia. The clinical features of subcortical aphasia are not uniform. Some authors divide this syndrome in two groups, anterior and posterior syndromes. Patients with the anterior syndrome, due to striatocapsular stroke, have a non-fluent, dysarthric, paraphasic speech with varying degrees of comprehension, naming and repetition. Right hemiparesis is often present. In the posterior syndrome, secondary to thalamic stroke, mutism and comprehension deficits are initially present. During recovery, spontaneous speech may be reduced, or, more rarely, fluent and paraphasic with jargons. Reading and writing may be affected or not. Some patients may present transcortical sensory aphasia. However, this categorization of subcortical aphasia may be too simplistic and different features have been reported after specific (head of caudate nucleus, tuberothalamic artery territory) subcortical lesions [6].

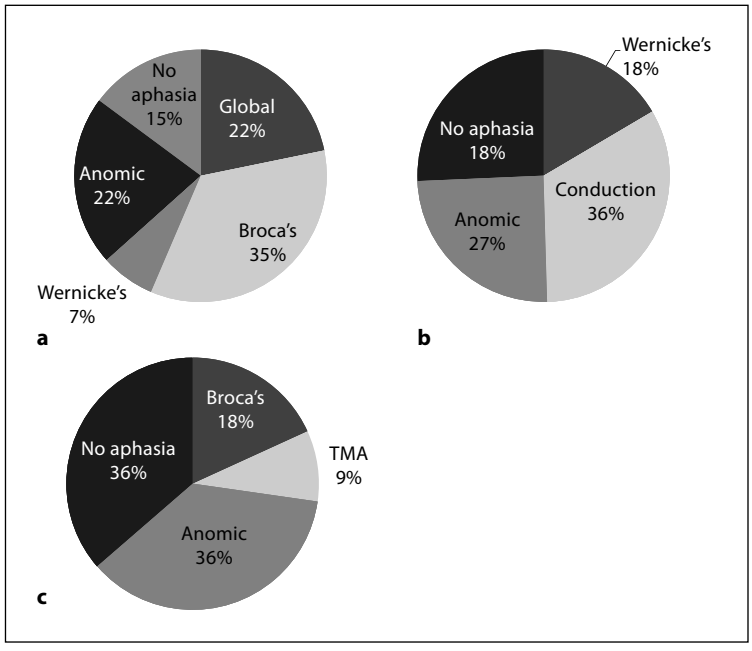

Fig. 1. Change in type of aphasia in survivors evaluated 1 year after acute stroke. Global (**a**), Wernicke's (**b**), and Broca's (**c**) aphasia at admission. TMA = Transcortical motor aphasia [2].

Other Disturbances

Pure 'Word' Deafness. In this rare syndrome there is an impairment of auditory comprehension and repetition, but non-verbal hearing, spontaneous writing and comprehension of written language are normal. Bilateral damage of the superior temporal gyri is the probable anatomical substratum of the syndrome.

Alexia without Agraphia (Pure 'Word' Blindness, Pure Alexia). It is a disconnection syndrome characterized by impairment in reading but with spared writing and recognition of words spelled aloud. It results from occlusion of the left PCA with infarction of the left occipital cortex and spleniun of the corpus callosum. Due to right hemianopia, all visual information is processed in the right occipital cortex and cannot be transferred to language areas in the left hemisphere because of the lesion in the corpus callosum. Some patients with this syndrome may be unable to name objects presented visually but can do it from tactile exploration.

Foreign Accent Syndrome. This is a rare disorder characterized by the emergence of new prosodic features that listeners perceive as a foreign accent and is usually due to left hemisphere lesion [7].

Recovery

Early recovery of aphasia is likely to be secondary to restoration of flow, while later stages may be linked to reorganization of structure [4]. In one study, about 40% of the patients with aphasia in the acute stroke phase presented almost complete recovery in 1 year and those who still had language disturbances presented a milder form (fig. 1) [2]. The change is always from non-fluent to fluent, never the reverse. A significant number of patients with global aphasia at admission present Broca's aphasia later.

Treatment

A recent review supports the effectiveness of speech and language therapy for people with aphasia following stroke [8]. Studies of pharmacotherapy for aphasia have focused on four drugs:

bromocriptine, amphetamines, piracetam and donepezil. Although preliminary evidence with some of these drugs is encouraging, randomized controlled trials are necessary. Transcranial magnetic stimulation is also being investigated as a method of enhancing aphasia recovery.

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Confusion, Agitation and Delirium

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Abstract

Delirium is one of the most serious and common complications that up to one third of older patients admitted to hospital develop. It is characterized by a disturbance of consciousness, decreased attention, and disorganized thinking that develops over a short period of time, and fluctuates during the course of the day. Delirium post-stroke prevalence ranges from 13 to 48% in general hospitals, and from 10.1 to 28% in Stroke Units. The Confusion Assessment Method and the Delirium Rating Scale are used as delirium screening tools. The cause of delirium is likely to be multifactorial. In stroke, reduced perfusion of the brain with hypoxia, which deranges neurotransmission, may be the cause. Delirium is more frequent after intracerebral hemorrhage and infarction in specific brain areas. Delirium without other signs of stroke has been reported more often after right-sided than after left-sided lesions. Age, cognitive decline, and multiple coexisting conditions are the most consistent and important risk factors for delirium post-stroke. Haloperidol is currently used as the drug of choice, if sedation is needed.

Delirium – Definition and Prevalence

Delirium is one of the most serious and common complications that up to one third of older patients admitted to hospital develop. Few studies have investigated the association between delirium and stroke, giving conflicting results with prevalence estimates ranging from 13 to 48% [1]. Studies which prospectively assessed delirium in Stroke Units found a lower delirium prevalence (range 10.1–28%) [2–4]. Delirium may be the only observable neurological abnormality and yet may indicate focal brain damage rather than a general toxic or metabolic abnormality [5]. It is characterized by a disturbance of consciousness, decreased attention, and disorganized thinking or a change in cognition that develops over a short period of time and fluctuates during the course of the day [6].

Delirium is frequently divided into hyperactive, hypoactive, and mixed syndromes. Hyperactive delirium is characterized by increased motor activity, logorrhea, stereotyped activities, and increased reactivity with aggressive behavior. Hypoactive delirium is the most common form in elderly patients and is characterized by reduced motor behavior, lethargy, speech retardation, diminished facial expression/perplexity, mental slowness, and diminished reactivity [1, 7].

Diagnosis

Abnormalities of thinking, perception and memory will usually be found in delirious patients: disorientation to time and place, impaired immediate, recent, and remote memory, dysnomia, agraphia, and visual-spatial dysfunction. Much of the difficulty with perceptual function and speech output relates to the inability to sustain attention

to the task at hand. Illusions, hallucinations, and delusions may also be prominent. Sleep-wake patterns are usually abnormal with inversion of the cycle. Autonomic hyperactivity features are also found. Delirious patients may quickly shift from hyperactivity to reduced activity.

Although the Mini Mental State Examination (MMSE) is a commonly used test to screen for cognitive impairment in routine clinical care, it was not designed to distinguish between delirium and dementia. The MMSE is influenced by factors such as language, mood and sensory/motor function, rendering it unsuitable in the acute stroke setting. The two most commonly used screening tools for delirium are the Confusion Assessment Method (CAM) and the Delirium Rating Scale (DRS) [1, 4, 7]. The CAM has a high sensitivity and specificity in general medical inpatients and is used by general health professionals [1]. An intensive care unit validated CAM may be used in case of severe aphasia [7]. The DRS, usually recommended after a positive screening with CAM, is intended for use by medical staff with specific training. It assesses the sleep-wake cycle and estimates delirium's severity [1, 7]. When pre-stroke cognitive impairment is suspected, patients are also screened using the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) or its shortened version [1, 2, 4]. None of the mentioned scores were validated for the acute stroke setting.

Neuropathophysiology of Delirium Post-Stroke

Although it has numerous potential precipitating factors (including stroke), the clinical presentation of delirium is generally similar, suggesting a common pathway in its pathogenesis, which remains poorly understood [1, 5]. Delirium is associated with generalized electroencephalogram slowing, consistent with widespread cortical dysfunction. These alterations may also be present in subclinical delirium or after clinical improvement. They are not distinctive of any delirium type [1, 7].

The most studied mechanisms involved in delirium are: altered neurotransmitters (mainly acetylcholine, dopamine, serotonin, noradrenaline, GABA, glutamate); altered hypothalamic-pituitary-adrenal axis (hypercortisolism); cytokine production, like interleukins-1 -2 and -6, tumor necrosis factor-α and interferon; alterations to the blood-brain barrier and oxidative stress [1, 7–9]. Despite these different pathophysiological hypotheses of delirium, the cause is likely to be multifactorial. In stroke, reduced perfusion of the brain with hypoxia which again deranges neurotransmission may be the cause [1].

The non-dominant hemisphere has a critical role in spatial and bodily perception and orientation, involved in perceiving emotion and in attentional processes. Disturbance of both spatial and emotional orientation might increase the risk of delirium, due to misinterpretation of the environment. Lesions in the right inferior parietal lobule may cause agitated confusion by impairing a patient's ability to selectively direct attention and ignore irrelevant stimuli [1, 2, 5].

Risk Factors

Delirium is more frequent after specific stroke types: intracerebral hemorrhage and infarction of the total anterior circulation, posterior cerebral arteries, especially in thalamus, capsular genu, caudate nucleus, hippocampus, fusiform and lingual gyri [1, 2, 5, 7]. Delirium without other signs of stroke has been reported more often after right-sided than after left-sided lesions, specifically the territory of the right middle cerebral artery [1, 5].

Several studies have examined potential risk factors in addition to stroke characteristics: the area of brain affected, the extent, the type of stroke, the extent of cerebral hypoperfusion and cerebral edema after stroke. These specific predisposing and risk factors include: old age, male gender, previous dementia or cognitive impairment, severe illness, especially intensive care unit treatment, depression, alcohol excess, physical frailty,

polypharmacy, malnutrition, renal impairment, dehydration, extensive motor impairment, low activities of daily living, apnea-related hypoxemia, neglect, brain atrophy, unsafe swallow, elevated admission C-reactive protein, apraxia, and impaired vision or audition [1–4, 7]. The impact of these factors varies in different studies. Age, cognitive decline, and multiple coexisting conditions are the most consistent and important risk factors in the literature. In most cases, delirium is a multifactorial syndrome resulting from the interaction of vulnerability on the part of the patient and hospital-related insults. The risk of delirium increases with the number of risk factors present [10].

Prevention, Treatment and Outcome

The development of delirium post-stroke has grave prognostic implications [1, 2, 4, 5]. There are no intervention data in prevention or treatment of delirium post-stroke though. Delirious patients have higher mortality, longer length of stay in hospital and higher risk of institutionalization than stroke patients without delirium [4]. This is worst in hypoactive delirium, being more likely to develop pressure sores or hospital-acquired infections. Patients with the hyperactive type have a better outcome than patients with the hypoactive type, probably because of early recognition and treatment. Falls are more likely in patients with hyperactive delirium though [5, 7]. Patients with normal premorbid cognitive and physical functioning have the most favorable prognosis for recovery [6]. Identifying patients at risk should make effective primary prevention possible. Inouye et al. [10] successfully implemented some non-pharmacological preventive approaches: multicomponent intervention targeting cognitive impairment, sleep deprivation, immobility, visual and hearing impairment and dehydration.

Once delirium is established in a stroke patient, treatment of the underlying cause should follow. For the hyperactive delirium, haloperidol is currently used as the drug of choice if sedation is needed. Risperidone, olanzapine, quetiapine and aripiprazole may be used instead of haloperidol, but experience with these drugs in the treatment of stroke-related delirium is still limited. Benzodiazepine treatment is reserved for delirium caused by alcohol withdrawal, indication of sedative-hypnotic drugs, or in case of hepatic failure [6].

Stroke Units implement a multidisciplinary approach in stroke patients aiming at the reduction of stroke complications, which are also beneficial for preventing delirium complications [3]. Patients with delirium should benefit from a quiet, comfortable environment with stimuli to maintain orientation, limiting room and staff changes, involving family members in supportive care, an uninterrupted period of sleep during the night, and encouragement of normal sleep-wake cycles [7]. Restraints should only be used in case of extreme agitation or aggression. The pharmacologic treatment of hypoactive delirium is still in debate but generally is not indicated. Different acetylcholinesterase inhibitors have been used in the management of delirium in stroke patients, but further research is necessary [7, 8]. Duration of delirium in stroke patients has not been prospectively established in long follow-up studies. Oldenbeuving et al. [8] report that the mean duration of delirium was 6.7 days (range 2–17).

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Executive Dysfunctions and Frontal Syndromes

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Abstract

Executive functions refer to a set of higher-level abilities that regulate and control human goal-directed complex behavior. These functions are a central component of the highest level of hierarchical cognitive-behavioral functioning. The theoretical construct of an executive system, its subcomponents, and the variables that measure them are not clearly defined. The term *executive function* is commonly associated with frontal lobe function, although it is not exclusive to the frontal cortex and extends to other regions of the brain. The executive system includes higher cognitive, behavioral self-regulatory, and metacognitive functions.

In contemporary literature, the theoretical descriptive construct executive system refers to a set of the following psychological functions which purpose is to manage and control human behavior [1–5]: (1) *Executive cognitive functions:* controlling attention (selective and divided), working memory, abstract thinking, problem-solving, strategic memory processes (active retrieval and selection of information, strategic memorizing), planning, set shifting, cognitive flexibility (the ability to switch rapidly between different response sets), metacognitive functions (self-awareness, self-control, social cognition). (2) *Executive behavioral functions* (sometimes called emotional/motivational self-regulatory functions: ability to initiate purposeful behavior, ability to sustain action to achieve the final goal, inhibiting stereotypic and drive reactions, affective and social adjustment.

Central functions that control other abilities must be integrated with adequate and adjusted emotional states and with more instrumental functions, such as language, perception, memory, praxis, etc.

Despite extensive literature on the subject, the concept of executive function/system, its subcomponents, and the variables that measure them are not clearly defined [6]. Now, the fundamental question is whether there is a single unitary superior ability that explains all the components of executive functioning or whether these components constitute distinct, although related, processes. Some authors believe in the existence of a unifying, central factor underlying executive functioning, i.e. general intelligence or working memory. Other authors suggest that many frontal (executive) functions exist and provide some evidence that they depend on multiple, separable control processes, although some of them are correlated with one another.

Neuroimaging methods have confirmed that the frontal lobes are primarily activated when engaging in so-called executive tasks [e.g. 7–9]. Homogeneous involvement of the prefrontal cortex was previously suggested, yet it is now accepted that executive functions are associated with

different regions of the frontal lobes and are distributed over a neuronal network including the parietal cortex, subcortical structures, and thalamic pathways. Three neural circuits involving the prefrontal cortex, the basal ganglia, and the thalamus have been identified as important for performance of executive control functions [1]. It is commonly accepted that the integrity of many brain structures is necessary for effective performance of goal-directed behavior and dominance of prefrontal-subcortical circuits is thought to be responsible for the highest level of hierarchical cognitive-behavioral functioning.

Historically, Baddeley [10] first coined the term *dysexecutive syndrome* and proposed to replace it with the anatomically associated term *frontal lobe syndrome*. Currently, many researchers and clinical practitioners use the term *frontal functions* as a synonym for *executive functions*, without objective reference to anatomy, yet the relationship between executive functions or frontal lobe functions is not quite clear. *Dysexecutive syndrome* seems to be more popular and is now preferred. It is divided into three distinct variants depending on the brain injury site. Such a distinction is compatible with anatomical/functional dissociations within the prefrontal cortex, in which orbitofrontal, dorsolateral, and medial regions are separated. Although theoretically damage to each region causes quite different clinical syndromes, the differences may not be clear in practice.

Patients with orbitofrontal cortex injuries usually demonstrate behavioral-emotional self-regulatory dysfunctions: personality alterations, disinhibition (socially inappropriate behavior), poor social reasoning and judgment, impulsivity, limited prediction of the consequences of their behavior, impaired controlling of affective behavior, unconcern (emotional blunting), emotional lability, lack of empathy (inability to perceive another person's emotional point of view), difficulty in making decisions, and the inability to appreciate humor. They are frequently dependent on environmental stimuli and can demonstrate stereotypic and utilization behavior, as well as limited self-awareness and self-reflection. Self-awareness implies a metacognitive representation of one's own mental and physical states, beliefs, and attitudes and is necessary to understand one's own thoughts and external events. The ability to understand the states of others comes also from self-knowledge.

Dorsolateral prefrontal cortex damage causes mainly executive cognitive dysfunctions demonstrating in impairment of attention, working memory, strategic information generation, planning and organizing volitional goal-directed multistep actions. Such patients are unable to cope with new problem-solving, use inappropriate rules, sometimes perseverate, and are unable to suppress automatic, overlearned responses. A deficit in divided attention is especially common (e.g. revealed in testing using a dual-task paradigm), which is frequently combined with the inability to sustain attention and maintain ongoing activity. A working memory deficit implies difficulties in temporary storage and cognitive manipulation of information necessary for performing complex tasks. The other memory deficits are hypothetically interpreted as impairments of flexible strategic memory processes involving active retrieval and selection of information required (e.g. difficulty in strategic penetration of lexical/semantic/phonological information during the verbal fluency task).

In patients with medial frontal cortex damage (involving the supplementary motor area and the anterior cingulate cortex), behavioral manifestations of executive dysfunction include global hypoactivity, loss of initiation and interests, and reduction in self-triggered activities and those triggered by the environment. It can be clinically expressed as apathy, aspontaneity, abulia (a reduction of movement and speech, difficulty in sustaining complex activities), or even akinetic mutism (in severe, usually medial frontal injuries on both sides). These latter states are sometimes used interchangeably in practice, although they differ

in the degree of deficit and are hypothetically related to diminished motivational factors of volitional behavior or an autoactivation deficit.

Executive dysfunctions are quite common in post-stroke patients and are considered to be the most disabling symptoms [11]. These deficits are frequent even in individuals experiencing ischemic or hemorrhagic strokes that did not structurally injure the frontal lobes, but rather disturbed the prefrontal-subcortical functional circuits. Control and management dysfunctions might have been observed in clinical practice, for example in patients having a stroke in the middle artery (restricted to the superior-anterior branch), anterior cerebral artery, or anterior thalamus (paramedian and tuberothalamic arteries). Dorsolateral prefrontal syndrome, in patients following lobar hemorrhage or watershed infarct, may vary according to the lesion laterality, for example interfering with language in left-sided lesions. Medial prefrontal syndrome may result from occlusion of the anterior cerebral artery, from spasm after rupture of an anterior communicating artery aneurysm, or from bilateral lenticulostriate infarct. Orbitofrontal executive syndrome may be a consequence of vascular events within orbitofrontal and prefrontal arteries. Issues related to the vascular etiology of executive dysfunctions are discussed in more detail in the review by Godefroy and Stuss [2].

Theoretically, executive deficits are most detectable in non-routine situations, demanding special attentional control, innovative thinking, and managing multiple tasks simultaneously. In clinical practice, detection may be hampered because an impairment of the executive system can result in a variety of behaviors while a specific behavior can be generated by a variety of impaired processes assigned to different levels of brain organization. Due to the complexity and variability of clinical problems, a single neuropsychological test cannot assess the executive system as a whole. Executive test tasks are multifactorial and subjects with lesions in different brain areas may achieve poor results in such tests due to various primary or secondary impairments. This is a major reason for the controversy regarding the validity of so-called executive/frontal lobe tests. As mentioned, controversy concerning the formal definition of executive functions leads to additional difficulties in measuring them. Until newer, better methods are developed and there is an adequate to modern understanding of these cognitive-behavioral variables, clinicians must also rely on tests previously designed to assess frontal lobe functions. Jurado and Rosselli [6] discussed the following obstacles in obtaining reliable measures of executive functioning: (1) difficulty in distinguishing between automatic and voluntary controlled actions and establishing what is really the novel problem for the subject; (2) execution of the task believed to measure executive functions might be triggering non-executive processes (to establish that some deficits presented by the patient are effects of executive system impairment, one must be able to indentify practically all other non-executive contributions to the task); (3) due to the modular nature of executive functions, similar observed behaviors can have quite different causes and executive functions show a low correspondence between process and behavior; (4) summary or endpoint test scores do not facilitate the isolation and quantification of specific features of executive functions such as planning, reasoning, problem-solving, attention control, etc., and (5) the poor ecological validity of tests of executive functions does not allow for accurate prediction of the individual's functioning in real life.

The presence and degree of persistent, long-term cognitive-behavioral deficits primarily depend on the site and volume of brain damage. In some patients executive dysfunctions gradually subside spontaneously but in others may be permanent consequences of stroke, disrupting effective social and vocational functioning.

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Memory Dysfunction

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Abstract

Memory is the cognitive ability that allows to acquire, store and recall information; its dysfunction is called amnesia and can be a presentation of unilateral ischemic stroke in the territory of the posterior cerebral and anterior choroidal artery as well as subarachnoid hemorrhage.

Memory is the cognitive ability that allows humans to encode, store and retrieve information. This can be classified according to time of retention (short- and long-term memory) and type of material and encoding (declarative and procedural) [1, 2]. Short-term memory allows to retain a limited amount of information over a limited time (e.g. the memory used to dial a telephone number after reading it) [1]. According to Baddeley's theory [3], short-term memory comprehends three components: the 'central executive system', a system to encode verbal material (phonological loop), and a system to encode visuospatial material (visuospatial scratch pad). The central executive system, involved in attention and abstract reasoning, controls both the phonological loop and the visuospatial scratch pad and has been associated with functioning of prefrontal areas [4]. A phonological loop disruption and thus difficulties in retaining verbal information has been associated with left inferior parietal lesion; while impairment in recalling short-term visuospatial material has been associated with right posterior parietal lesion [5]. On the other hand, long-term memory allows to recall a large amount of information over a very long period (e.g. memory of a fourth birthday for an octogenarian) and has been related with hippocampus and adjacent cortex including entorhinal, perirhinal, and parahippocampal gyri [6].

Declarative memory requires conscious encoding and recall; it comprehends episodic and semantic memory [7]. The former store information of a specific time and place (e.g. memory of having eaten an ice-cream in Paris last year); while the latter is our conceptual knowledge about the world (e.g. information about algebra, history, geography. . .). Procedural memory is involved in conditioning, priming and learning new movements or sequences (e.g. learning to ride a bicycle). Episodic memory has been related with medial temporal lobe functioning while semantic and procedural memory have been respectively associated with lateral temporal lobe and cerebellum activity [8–10]. Amnesia is a memory impairment and has been frequently associated with posterior cerebral infarction, involving the medial temporal lobe and the thalamus, anterior choroidal infarction and subarachnoid hemorrhage [11, 12].

Medial Temporal Lobe Infarction

Occlusion of vessels from the P1 segment of the PCA produce infarction of the posterior hippocampus, parahippocampal and entorhinal cortex. Severe memory dysfunction is relatively common in unilateral stroke, especially when the left hemisphere is involved. Accompanying symptoms include visual field defect when the optic radiation or calcarine cortex are implicated as well as color anomia when mesial occipitotemporal junction ischemia is present. More extensive lesions could be associated with visual agnosia secondary to inferior temporo-occipital ischemia or alexia without agraphia when occipital paraventricular white matter is infracted [13]. The memory dysfunction is often severe and generalized in the acute phase but might evolve in a more selective deficit such as verbal amnesia in a left hemisphere lesion or visuospatial amnesia in a right hemisphere lesion.

Thalamic Infarction

Memory deficits have also been associated with thalamic involvement of two of the four arterial groups, specifically the paramedian and tuberothalamic arteries. Both supply overlapping territories including the mamillothalamic tract, the ventroamygdalofugal pathway, and the dorsomedial nucleus, which are involved in memory formation and consolidation since they are connected to the hippocampus and amygdale [11].

Paramedian artery infarctions show decreased and fluctuating levels of consciousness in the acute phase followed by cognitive symptoms in the chronic phase, when amnesia and disorientation appear. Bilateral paramedian infarcts cause thalamic 'dementia', which consists of severe and permanent cognitive deficits; this picture may often be indistinguishable from neurodegenerative disorders. Common behavioral symptoms are utilization behavior, disinhibition, personality changes and abulia. Hemiparesis and hemiataxia might be present [14, 15].

The tuberothalamic infarction cause cognitive symptoms such as memory, time disorientation and acalculia. Language symptoms are very common and produce a clinical picture called *thalamic aphasia* characterized by anomia with decreased fluency, comprehension impairment, and fluent paraphasic speech with poor content. Right-side infarcts present with visual memory impairment and neglect [16]. Behavioral deficits include perseverations, apathy, abulia and anosoagnosia. Transitory motor, sensory signs and facial paresis for emotional movements have been described [16].

Anterior Choroidal Artery

Only very few cases of anterior choroidal artery unilateral ischemic stroke exhibit with persistent and predominant memory impairment; of these cases, two had left thalamus lesions and one left anteromesial temporal lesion [11]. More often, memory loss is associated to the more classical presentation of anterior choroidal artery including visual field defect, motor and sensory loss; these cases usually have a larger lesion which also involves the posterior limb and genu of the left internal capsule.

Subarachnoid Hemorrhage

Subarachnoid hemorrhage frequently causes generalized cognitive dysfunction including memory loss caused by secondary infarction [12]. Memory dysfunction has been more likely associated with ruptured aneurysm in the anterior communicating and posterior communicating arteries. The former shows confusion and denial in the acute phase, while apathy and amnesia become evident in the chronic phase. The latter was present with predominant amnesic syndrome without behavioral symptoms [17].

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Neurobehavioral Syndromes

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Abstract

Dysfunction of higher cortical function and neurobehavioral syndromes may be present in up to 87% of stroke patients. These symptoms may occur less often in patients with transient ischemic attacks (36%). Approximately 22% of stroke patients may present only with cognitive and neurobehavioral symptoms without elementary neurological deficits. In this chapter we concentrate on delusions, hallucinations, misidentification syndromes, anosognosia of hemiplegia, aggressive behavior and also extended self syndrome.

Delusions

Delusions are beliefs with which a person is preoccupied and to which the person firmly holds, despite their logical absurdity and lack of supporting evidence [1]. Delusions can be found in approximately 4% of stroke patients [2]. In stroke patients with delusions the ischemic lesion is most often localized in the right temporal lobe, especially in the inferior right middle cerebral artery territory [2, 3]. Content of delusions may include jealousy, suspicion, persecution, etc. [2]. In some patients delusions may lead to misidentification of people. Capgras syndrome is one of misidentification syndromes in which patients may recognize family members as imposters, aliens. These delusions are not directed to everyone and they seem to be more orientated on people who are in an emotional bond with the patient (family members) [3]. Spiegel et al. [4] describe a female patient with left anterior cerebral artery infarction who claimed that her attending physician was an imposter and that she was not in a real hospital but in an annex. Another misidentification is Frégoli syndrome in which the patient may believe that one or more familiar persons repeatedly change their appearance and that these persons are imposing a direct threat to the patient. De Pauw et al. [5] reported one case of proven cerebral infarction and occurrence of Frégoli syndrome. Cotard's delusion relates to nihilistic belief of non-existence of self and the external world (Cotard's original definition of *'le délire de négation*'). Patients may believe that their body is rotting, putrefying and malodorous and that they lost their blood or internal organs [6]. In a case series of 100 patients with Cotard's syndrome, depression was reported in 89% of the subjects. Among the most common nihilistic delusions, 86% were related to the body and 69% concerned existence [7]. The reduplicative paramnesia (Pick's syndrome) is known as spatial delirium *(délire des lieux)*. Patients may believe that familiar places, objects, or events are duplicated. There may be a delusional belief of being

in a different place than the current one. Moser et al. [8] reported one case of an 81-year-old male patient who presented with reduplication of an event rather than place or person related to a large right frontal lobe infarction. There is a case report of a 66-year-old woman with right middle cerebral artery occlusion who developed a delusion of misidentification for place as she believed that her car, furniture and house were duplicated [9]. There are other misidentification syndromes such as intermetamorphosis, temporal reduplication, autoscopic phenomena, and mirrored-self misidentification [10]. Intermetamorphosis is a delusion in which the patient thinks he/she has changed into another person without change in appearance. Reverse intermetamorphosis, except for mental change, includes physical change as well. Temporal reduplication leads to ongoing déjà vu phenomena as the affected person believes that new events had already happened in the past. Autoscopic phenomena are similar to Capgras syndrome and present with the patient considering him/herself an autoimposter. Mirrored-self misidentification presents as the patient's inability to recognize one's own reflected image. However, the capacity to recognize others in the mirror often remains intact [11].

Hallucinations

Hallucinations are rare and occur in patients with right hemispheric damage without a predominance of any etiological stroke subtypes [12]. Auditory hallucinations are very rare (less than 1% of patients). They are self-limited in duration and may disappear after a few months from onset of symptoms [13]. Visual hallucinations may be complex and they may involve the hemianoptic part of visual field (Charles-Bonnet syndrome). One of the hallmarks of this syndrome are 'liliput hallucinations' when characters or objects seem to be smaller than normal. These objects may have complex colored patterns and most often the objects seen are animate (people, animals, plants) [14]. Another rare type of visual phenomena constitutes of vivid, complex, stereotyped hallucinations occurring in the hemianoptic visual field. These symptoms may be encountered in patients with posterior cerebral artery ischemia [15]. Peduncular hallucinosis (Lhermitte's syndrome) is related to damage of the midbrain, thalamus, or rostral brainstem. The anatomical substrate for this particular type of hallucination seems to be the reticular part of the substantia nigra [16]. Visual hallucinations in this syndrome tend to be complex and naturalistic (e.g. motorbikes, dogs, etc.) [17]. Anton-Babinski's syndrome may occur in patients with sudden visual loss of any etiology from eye dysfunction to cortical blindness related to metabolic, toxic and vascular etiologies. Patients with this syndrome deny their visual disability and confabulate visual perception details. Maddula et al. [18] describe a case of an 83-year-old woman with bilateral occipital lobe ischemic strokes who was colliding with objects when walking and at the same time she denied visual loss and confabulated in the description of her surroundings. Klüver-Bucy syndrome was described in only 27 patients. By definition, this syndrome consists of visual agnosia, hypermetamorphosis, hyperorality, loss of normal fear and anger, indiscriminate hypersexuality and memory deficit [19]. Patients with this syndrome may face legal actions due to their behavior and may occasionally get imprisoned for uninvited physical contact with others [20]. In reports of human Klüver-Bucy syndrome the extent of brain involvement differs and there are cases of not full presentation of the syndrome. However, the importance of bilateral amygdala involvement was documented as well [19]. Müller et al. [21] reported a patient with severe amnesia, distractibility, hyperorality, and lack of affect control. Her social behavior was inappropriate. She was demonstrated to have bilateral infarctions in the territories supplied by both thalamoperforating arteries as confirmed with magnetic resonance imaging.

Anosognosia and Denial

Anosognosia refers to a situation where the patient does not acknowledge the disease [22]. The term denial refers to a positive or productive phenomenon compatible with a delusional disorder in which a patient actively negates the disease [23, 24]. The anatomical substrate for denial of illness is a destruction of non-dominant hemispheric structures including the inferior and posterior parietal lobe. Denial composes disorders of mental function, impaired proprioception and aberrant representation of body image [25]. Patients with denial of hemiplegia may deny contralateral weakness. Results of a recent meta-analysis show that denial for contralateral weakness is related to right-sided or bilateral brain lesions of both cortical and/or subcortical locations [26]. Vocat et al. [27] studied 58 patients with right hemispheric stroke with contralateral hemiparesis. Anosognosia for hemiplegia was found in 32% of patients in the hyperacute phase of stroke to fade away at 6 months to the level of 5%. The authors demonstrated a correlation between anosognosia and the severity of loss of proprioception, extrapersonal spatial neglect and disorientation.

Aggressive behavior is defined as a deliberate action to hurt/injure other individuals either in a direct physical way or indirectly (verbally, psychologically). An anatomical substrate for this type of an abnormal behavioral pattern is a disruption of limbic system function. Botez et al. [28] prospectively studied consecutive patients with first-ever ischemic stroke and found that 7.3% with posterior cerebral artery territory stroke presented with sudden onset of agitation and aggression that were triggered by external stimulation. Aggressive behavior manifested itself with swearing and biting other people [28].

Response-to-Next-Patient-Stimulation Syndrome (Extended Self Syndrome)

This syndrome was described in 1988 [29]. Eleven of 134 patients with a right hemisphere stroke responded to stimuli directed at other patients in the same room and the affected patients responded as if these stimuli were directed at them.

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Right Hemisphere Syndromes

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Abstract

Stroke is the leading cause of acquired motor disability in the adult. Neuropsychological sequelae are common after vascular brain injury. While left cortical signs and symptoms are clearly evident at neurological examination, right hemispheric dysfunction must be carefully pursued and sometimes can be underrecognized. Indeed, patients with right hemispheric strokes present later to an emergency department and have a lower chance of receiving intravenous recombinant tissue plasminogen activator. For a better comprehension of clinical signs and symptoms in right acute hemispheric stroke, in this chapter we present a review of the principle clinical syndromes.

Stroke is the leading cause of acquired motor disability in the adult. Neuropsychological sequelae are common after vascular brain injury. Clinical observations suggest that people affected by right hemispheric stroke (RHS) have a lower score when evaluated with the National Institutes of Health Stroke Scale (NIHSS) in respect to left hemispheric patients, this mainly for the burden of aphasia on total score. Neuroimaging studies have shown that the NIHSS is underpowered for assessing the severity of right hemisphere damage in the acute phase of stroke [1]. While left cortical signs and symptoms are clearly evident at neurological examination, right hemispheric dysfunction must be carefully pursued and sometimes can be underrecognized [2]. Indeed, patients with RHSs present later to an emergency department [3, 4] and have a lower chance of receiving intravenous recombinant tissue plasminogen activator [3].

Although the right hemisphere is often called the non-dominant one, it has a key role in cognitive function such as spatial orientation, timing, time perception, coordinated motor behavior, recognition of objects and faces; in emotional functions such as prosody, empathy and comprehension of emotionality, affective behavior, wit and humor; in attentional function like arousal, vigilance, attentivenes (right and left space); in symbolic representation and in frontal lobe functions: planning, volition, social conduct and executive control. Most of the time it can be difficult to evaluate right hemisphere deficits at the bedside. It is easier to observe abnormal behavior like anosodiaphoria, also called the 'belle indifference', first described by Babinski in 1914.

Neglect is the commonest behavioral syndrome in right post-stroke patients. The reported incidence is up to 82% after right-hemisphere stroke and to 65% after left-hemisphere stroke [5]. Neglect is a predictor of poor motor recovery and higher disability [6–8]. It is associated with falls, longer of hospital stay and less likelihood of being discharged home [9]. It has been defined as

an impairment in attention or response to stimuli in the hemispace contralateral to the lesion, not attributable to a primary sensory or motor deficit [9, 10] or again as the inability to report events occurring in the side of space contralateral to the damaged hemisphere, to orient toward, and to explore, by motor actions, that side of space [11]. Neglect can be classified by the distribution of the pathological behavior into spatial or personal neglect or again be described by the modality in which can be elicited (sensory, motor or representational) [12]. The term spatial neglect should refer to a failure to acknowledge stimuli on the contralesional side of the space [13]. It can be subdivided into: peripersonal neglect, where pathological behavior is confined within the reaching space, and extrapersonal neglect in which the deficit involves the far space [14]. Personal neglect is the lack of awareness of the side of the body opposite the brain lesion [15]. Neglect can be present alone or be associated with multiple neuropsychological deficits. The frequency of neglect can differ in case series according to the specific neuropsychological test used and to the timing of evaluation [16]. There are many different pen-and-paper tests available for the evaluation of right stroke patients such as line bisection tests, cancellation tests, copying and drawing tests, behavioral inattention test, semistructured scale for functional evaluation of hemi-inattention and the Catherine Bergego Scale [17]. Neuropsychological studies have shown that several tests are more likely to uncover evidence of neglect than a single test. Behavioral assessment of neglect in daily life is more sensitive than any other single measure of neglect [16].

Different brain target lesions can result in neglect in the acute/subacute phase of stroke: superior and middle temporal gyrus, the inferior parietal lobule, insula, inferior frontal gyrus and the rolandic operculum; at the subcortical level: basal ganglia as well as the white matter fiber tracts, superior longitudinal fasciculus, superior occipitofrontal fasciculus and inferior occipitofrontal fasciculus. Karnath et al. [18] found that cortical damage of the superior and middle temporal gyri as well as subcortical injury of the basal ganglia (putamen) and the white matter fiber tracks inferior occipitofrontal fasciculus and uncinate fasciculus are critically related to the emergence of chronic spatial neglect. When coming for a neurological examination, people affected by RHS usually present head and skew deviation on the right: it has been suggested that the eye-in-head position in clinical magnetic resonance imaging or computed tomography scans obtained at admission shows a specific relationship to spatial neglect [19]. A tight link between spatial neglect and the ipsilesional deviation of eyes is also suggested by the observation that both signs recover in parallel [20]. In a recent paper by Becker and Karnath [19], the eye-in-head position was evaluated in a series of 124 consecutive patients with first-ever left or right stroke. They found that the degree of eye deviation towards the ipsilesional side was significantly larger in the patients with spatial neglect than the brain-damaged subjects without the disorder and concluded that pronounced eye-in-head deviation towards the ipsilesional side on clinical brain scans seems to be associated with spatial neglect rather than with brain damage per se. Left hemiplegia, hemianesthesia and hemianopsia are frequently observed in the acute phase. Occasionally, eye opening apraxia can be detected [21, 22]. During the evaluation of a right-sided stroke patient, motor neglect should be pursued. Indeed it is a common disorder but often underrecognized and can contrast motor recovery. There are no routine clinical tests that take into account the presence of the disorder; it has been defined as 'an underutilization of one side, without defects on strength, reflexes or sensibility' [23]. In these patients, spontaneous movements of the affected body can be lacking, but still can be evoked when patients are strongly encouraged to use it.

Anosognosia, literally 'no illness knowledge', affects the awareness of cognitive, emotional and physical sequelae. Anosognosia for hemiplegia is a common finding in right-sided stroke patients. Its prevalence rates from 20 to 44% depending on the time elapsed since brain injury [24]. 'These patients deny their deficit, and overestimate their abilities, they state that they are capable of moving their paretic limb and that they are not different than normal people. If they partially admit impairments, they will ascribe them to other causes (i.e. arthritis, tiredness, etc.)' [19]. In case series, lesion analysis revealed a correlation between anosognosia for motor impairment and vascular lesion of the anterior part of the insula, inferior motor areas, basal ganglia structures, limbic structure and deep white matter [25]. Many theories have been proposed to clarify the nature of the phenomenon such as a global cognitive impairment, a difficulty in integrating or transferring short-term memory experiences into long-term memory schemata or again a loss on proprioception [25]. Stroke severity appears higher in anosognosic patients [26]. There are some structured interviews for the evaluation of anosognosia for hemiplegia [27].

Agnosia for body parts is an intriguing self-related disorder that can be observed after a right brain injury. The term asomatognosia was introduced by Critchley in 1953 in the description of 'loss of awareness of one body half'. The usual clinical presentation of asomatognosia is the non-recognition and the denial of ownership of the left arm. The degree of asomatognosic behavior can differ among patients. Some appear simply unaware of, or confused regarding ownership of the limb. They may mistake their arm with the examiner's arm or simply profess ignorance to whom the arm belongs [28]. Some others manifest pathological elaboration of the proprioceptive input from the left side of the body. In 1942, Gerstman introduced the term 'somatoparaphrenia' to describe the 'illusion or distortions concerning the perception of and confabulations or delusions referring to the affected limb or side'. These patients 'adamantly insist that the arm is not their own, despite irrefutable proof that the arm is attached to the body, and the patient produces elaborate confabulations as to how the arm got there or who it really belongs to' [28]. In a recent review, Vallar and Ronchi [29] confirmed that somatoparaphrenia is frequently associated with right hemisphere damage more than extrapersonal spatial neglect, concluding that the sense of body identity and ownership are largely right hemisphere-based. It has been suggested as a key role of vascular lesions of posterior cerebral regions (temporoparietal junction), on posterior insula [30] and basal ganglia on the genesis of the somatoparaphrenia [31]. Another recent paper pointed out the role of medial prefrontal cortex: this is one of the heteromodal association cortical regions with the limbic functions of the maintenance of homeostasis and the conditions of the internal milieu. Since this region is intimately concerned with distinguishing the self from the world, damage to this system could cause confusion between the internal representation of the self and external stimuli and contribute to asomatognostic response [28]. Between the abnormalities of corporeal awareness, misoplegia is a rare but fascinating disorder and appears to be the antithesis of excessive concern. This phenomenon is characterized by dislike, amounting to hatred of the affected part, often accompanied by verbal or physical abuse; in these patients frankly psychotic types of thinking and behavior may develop. Indeed, RHS leads to several neuropsychiatric disturbances often unrecognized like depression, emotional incontinence, apathy and alexithymia. In a recent paper a preliminary explanation of the mechanism underlying these emotional changes has been proposed: damage to the right anterior cingulate cortex could lead to emotional blunting and ineffective modulation of emotional responses due to the disruption of frontal-thalamic-cerebellar networks [32].

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Post-Stroke Dementia and Cognitive Impairment

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Abstract

The term post-stroke dementia (PSD) is used to define any dementia occurring after stroke irrespective if the leading cause is vascular, degenerative or mixed. PSD is a frequent condition after stroke and its prevalence ranges from 6 to 32%. However, not all cognitive impairment cases following a stroke are enough severe to fit the criteria for dementia. Indeed, many patients after a stroke develop mild cognitive impairment that in some cases can progress to PSD. There is an urgent need to find sensitive tools to detect post-stroke cognitive impairment as early as possible. The detection of cognitive impairment in the acute phase of stroke can offer valid information to the clinician on whether to set an early cognitive rehabilitation and to plan a more focused follow-up.

Stroke is a risk factor for dementia and dementia predisposes to stroke [1]. Several studies have demonstrated that dementia is far more frequent in stroke patients than age- and sex-matched controls. The term post-stroke dementia (PSD) is used to define any dementia occurring after stroke irrespective if the leading cause is vascular, degenerative or mixed [2]. Although vascular dementia is a direct consequence of cerebrovascular diseases (cortical and lacunar infarcts, white matter changes and hemorrhages), not all demented patients who have had a stroke have vascular dementia. This concept is very important in clinical practice because patients who are followed up after stroke can be diagnosed as either with vascular, degenerative or mixed dementia. Moreover, when vascular lesions or neurodegenerative diseases do not lead to dementia by themselves, their cumulative effect can reach the threshold of lesions required to produce dementia [3].

According to a classical view, the main cerebrovascular pathologic processes associated with PSD are multiple large cortical infarcts, single infarcts localized in functionally important areas and lastly, multiple lacunar infarcts, and intracerebral hemorrhages [4].

Epidemiology of PSD

Prevalence and Incidence. The prevalence of dementia among people with a history of stroke is similar to that seen in subjects 10 years older without a history of stroke [5]. Depending on the population studied, the criteria used for the diagnosis of dementia, and the time interval between stroke and the neuropsychological assessment, the prevalence of PSD ranges from 6 to 32% [6]. These discrepancies may be also related to other methodological differences, for example the exclusion of patients with severe aphasia or with pre-stroke cognitive impairment may underestimate the prevalence of dementia [7]. The prevalence rates of PSD from cohorts of stroke patients are reported in table 1 [8–16].

Table 1. Prevalence of PSD in different stroke cohorts

Reference (first author)	Months from stroke onset	n	Population	Diagnostic criteria	Prevalence %
Pohjasvaara 1998 [8]	3	337	ischemic stoke	DSM III	31.8
Censori 1996 [9]	3	110	first-ever ischemic stroke	NINDS-AIREN	13.6
Desmond 2000 [10]	3	453	ischemic stroke	DSM III R	26.3
Lin 2003 [11]	3	283	ischemic stroke, no previous TIA	ICD-10	9.2
Klimkowicz-Mrowiec 2006 [12]	3	190	stroke	DSM IV	22.6
Zhou 2004 [13]	3	434	ischemic stroke	DSM IV	27.2
Andersen 1996 [14]	6	220	first-ever stroke	Mattis Dementia Rating Scale	26.0
Hénon 2001 [15]	6	202	stroke	ICD-10	22.8
Inzitari 1998 [16]	12	339	stroke	Proxy-informant interview based on ICD-10	16.8
Hénon 2001 [15]	12	202	stroke	ICD-10	21.4
Hénon 2001 [15]	24	202	stroke	ICD-10	21.6

The incidence of dementia and stroke increase with age and it is estimated that in western countries one third of the population will experience dementia or stroke or both [17]. Several studies have confirmed that stroke doubles the probability of developing dementia and that risk is higher in the first 6–12 months [3]. One meta-analysis showed that the incidence of new dementia in patients with stroke versus controls was up to 9 times higher after one [18]. In a community-based study done over 25 years, the cumulative incidence of PSD was 7% after 1 year, 10% after 3 years, 15% after 5 years, 23% after 10 years, and 48% after 25 years [19]. The incidence of PSD may depend on whether preexisting cognitive impairment is included or not. A certain amount of PSD cases are not new-onset dementia but preexisting dementias that are revealed after stroke [2].

Clinical and Neuroimaging Predictors of PSD. If we consider demographic and clinical factors, older age, low educational attainment, previous cognitive decline, premorbid disability, and vascular risk factors such as diabetes and atrial fibrillation have been shown to be strongly associated with PSD [18]. Stroke characteristics such as dominant hemisphere strokes, dysphasia, hemiparesis, hemianopia, and neglect are associated with an increased risk of PSD [18]. Moreover, previous strokes and recurrent strokes are predictors of PSD. A recent study has demonstrated that infarcts in multiple areas are more likely than single infarcts or multiple infarcts in a single area to cause dementia [20]. In addition to the acute stroke lesion, several preexisting neuroimaging features such as silent infarcts [10], cortical cerebral atrophy [10], medial temporal lobe atrophy [21], and white matter changes [22] have been associated with an increased risk to develop PSD.

Post-Stroke Vascular Cognitive Impairment

In 1993, Hachinski and Bowler [23] reacted to the publication of the National Institute of Neurological Disorders and Stroke (NINDS) and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (AIREN) criteria for vascular dementia and strongly criticized the concept of vascular dementia; they proposed a radical modification

of the vascular dementia concept and introduced a new term, vascular cognitive impairment (VCI), to describe the large spectrum of the cognitive consequences of vascular diseases that include also the early stages of cognitive impairment. They also stressed the fact that vascular diseases may cause cognitive impairment with different physiopathological mechanisms and clinical profiles.

Accepted criteria for VCI are not yet available and the term has been used over the years with different meanings. A paper resulting from a consensus conference listed the following different expressions that can be enclosed in VCI: PSD, vascular dementia with all its subtypes, mixed and vascular mild cognitive impairment, and also the category of Alzheimer disease plus vascular dementia (so-called mixed dementia) [24].

As pointed out by Hachinski and Bowler [23], there are patients with VCI not severely enough affected to reach the level of dementia (this category can be globally referred to as vascular mild cognitive impairment). It is important to note, however, that likely not all the forms of vascular dementia are preceded by a mild cognitive impairment state, for example some patients at risk can abruptly develop vascular dementia in the case of a major or strategically located infarct [25]. Similarly, some patients after a stroke can develop mild cognitive impairment and a recent study has shown that vascular mild cognitive impairment is progressive because incident dementia was diagnosed in 24.4% after 3 years, giving a mean rate of approximately 8% per year [26].

Therefore, post-stroke VCI patients can be considered all those patients who develop cognitive impairment after stroke even if the cognitive impairment is not severe enough to fit the criteria of dementia.

Neuropsychological Assessment in Acute Phase of Stroke

Neuropsychological deficits are amongst the most common and incapacitating manifestations of stroke and in some circumstances may be the single or dominant manifestations of stroke [27]. In contrast, little attention has been paid to cognitive functioning in the early phase of stroke and one of the possible reasons for this is the uncertainty about the feasibility of a neuropsychological evaluation in the acute stage. In fact, several clinical conditions such as fluctuating level of arousal, psychological distress and headache, motor and visual deficits can hamper a cognitive examination in acute stroke [28].

Most of the neuropsychological tests used in the stroke population are focused on the detection of memory impairment with little attention to the evaluation of executive functions which are more frequently impaired in cerebrovascular diseases than in neurodegenerative diseases [29]. The neuropsychological tests proposed until now for the evaluation of the global cognitive functioning in the acute phase of stroke such as the Mini Mental Status Examination [30], the Stroke Unit Mental Examination [31], and the Rotterdam-CAMCOG [32] have demonstrated either a low sensitivity in detecting early cognitive deficits or a bad applicability in the acute clinical setting, particularly due to the length of the administration.

Recently, a new neuropsychological test, the Montreal Cognitive Assessment (MoCA test) [33], has been proposed in this particular clinical setting by a consensus paper published by the NINDS and the Canadian Stroke Network especially for its easiness of use at the bedside and its specificity in the evaluation of executive functions [34]. The MoCA test has been designed to be sensitive to mild cognitive impairment and may detect cognitive impairment after stroke or TIA, particularly in executive functions, attention and delayed recall [35].

Three studies have evaluated the different accuracy between the MoCA test and the MMSE in detecting cognitive impairment in the early or late stages after stroke [35–37]. They all showed that the MoCA test is feasible in detecting post-stroke cognitive impairment; in the study by Pendlebury

[35] over half of the patients with a MMSE score ≥27 were designated as cognitively impaired by the MoCA. However, a limitation of the use of the MoCA in this clinical setting is a low specificity compared with the gold standard, a comprehensive neuropsychological battery, in detecting post-stroke cognitive impairment [36]. The good sensitivity of the MoCA observed in several studies is mainly due to the choice of cut-off scores, favoring sensitivity at the cost of specificity [36]. To overcome this problem, Godefroy et al. [37] suggested the determination of a standard cut-off score in detecting post-stroke cognitive impairment patients which has to be refined in a larger sample representative of the general population. This cut-off has not been settled yet.

Conclusion

Approximately one third of patients will develop dementia after stroke. Not all patients will be so cognitively impaired to be diagnosed as demented. Nevertheless, mild cognitive deficits may have important consequences in social and affective life after stroke. There is an urgent need to find sensitive tools to detect post-stroke cognitive impairment as early as possible. Identification of mild and early cognitive deficits may have an important role in preventing the progression from mild cognitive impairment to PSD.

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Mood Disorders after Stroke

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Abstract

Mood disorders occurring after stroke are a major concern to public health as they are frequent, difficult to diagnose and to treat, and have high impact on the quality of life of patients and caregivers. The association of manic symptoms (rare) in the acute phase of stroke with strategic locations within the right hemisphere is clinically significant. However, the link among poststroke depression and anxiety (most prevalent), brain circuitries, clinical signs and individual psychological factors is not yet disentangled. The involvement of too many variables produces methodological difficulties and, therefore, the findings of a great number of studies are not systematically replicated. Thus, there is a need for research in this area of stroke medicine. Investigations on poststroke mood disorders might increase insight into the pathogenesis of mood disorders (which share the same clinical profile) occurring in people without brain lesions.

Poststroke Depression

Poststroke depression (PSD) is a disorder with high prevalence (33%) [1] over all stroke phases and high negative impact on participation to rehabilitation, daily activities, quality of life, survival of patients, caregiver burden and healthcare costs. PSD diagnosis is exclusively clinical but the clinical signs are too vague. There are no available neurobiological or neurophysiological markers and the insight into the pathogenic mechanisms is still poor. PSD lacks neuropathological studies and animal models. Over the last 40 years the main challenge in studying and treating PSD remains understanding and disengaging the role of biological from non-biological variables.

Diagnosis

Patients should be evaluated to diagnose and treat PSD early and late after stroke because the risk of PSD remains high lifelong. The best available diagnostic criteria for PSD are provided by the DSM-IV-TR, however the link between the depressed mood and stroke remains speculative. DSM-IV criteria include depressed mood and loss of interest or pleasure as the 'core' symptoms and additional symptoms (weight loss or gain, sleep changes, feeling restless, fatigue, worthlessness, inability to concentrate or decide, suicidal ideation). Core and additional symptoms should occur over a period of at least 2 weeks. The DSM-IV distinguishes between major and minor depression but it is uncertain whether this dichotomy is founded on different etiologies and outcomes. Furthermore, younger and elderly patients might show different clinical patterns of symptoms and early (first 3 months) and late (after 3 months) forms of PSD could correspond to different diseases [2]. While evaluating PSD, it is important to acquire some understanding of the patient's emotional life prior to stroke. Some of the patients diagnosed with PSD might suffer from prestroke depression. PSD diagnosis is often hampered by

several confounding signs of stroke that might mime or hide depressive changes and/or by other psychiatric disorders (anxiety, mania, personality changes and obsessive-compulsive changes) that can manifest together with PSD.

Scales and questionnaires (generally been validated with the DSM-IV criteria of depression) are important instruments as they engender reproducible diagnosis and allow monitoring of therapeutic interventions. However, not one of these tools is superior to the other [3] and the examiner should always judge and document the validity of patients' answers. Vegetative symptoms and fatigue might be the consequence of stroke rather than depressive equivalents. Whether they lead to overdiagnosis of PSD is a matter of debate. Proxy ratings and visual analogue mood scales could also engender unreliable results [3]. Up to 30% of all stroke patients may be excluded from assessment due to language or cognitive/perceptual impairments. Patients with spatial neglect might show altitudinal bias and prefer the top of self-report scales. Anosognosia (lack of awareness), anosodiaphoria (indifference to the deficit), alexithymia (difficulty in identifying and reporting feelings), unawareness of emotions, defective abstract thinking and magnitude estimation deficits undermine introspection into personal emotional experiences. Thus, the clinical diagnosis of PSD should basically include both extensive emotional/affective and detailed cognitive evaluation. Observable behaviors (e.g. crying, facial expressions, catastrophic reactions) might be alternative clinical markers of depression and the subject of future studies. For many patients, the use of several instruments and interviews of several informants, caregivers and healthcare professionals, including neuropsychiatrists and neuropsychologists, has to be encouraged.

Risk Factors and Pathogenesis

Several risk factors have been delineated across a multitude of studies, often with contradictory or inconclusive results. The most important factor is probably stroke severity [4, 5]. Available scientific evidence does not yet allow to formulate a comprehensive theory of PSD pathogenesis sufficiently predicting the occurrence of the disease. As the biological factors, the low incidence of depression with brainstem, cerebellar and occipital lesions supports the role of frontal and deep brain regions (basal ganglia and thalamus) with left hemisphere dominance [4, 6–8]. However, several other studies [9–12] did not suggest hemisphere lateralization or lesion preponderance within prefrontal regions and basal ganglia. FMRI studies with affective stimuli could be a new approach for neural localization of PSD as some recent findings indicate for endogenous depression [13]. There is still little information on biochemical or neurotransmittorial regional brain changes. Genetic factors might also intervene [14]. Depressive episodes are often temporally linked to precipitant events, especially when these imply loss of personal expectations. The role of non-specific psychological reactions to illness is suggested by similar prevalence and pattern of symptoms between PSD and depression occurring with other medical conditions [15].

Cognitive Impairment

A significant association between PSD and cognitive deficits has been reported in several studies [5], even though stroke itself may be followed by a significant impairment in cognitive performance [16]. Executive (attention, concentration, nonverbal problem-solving, and psychomotor speed) deficits are preponderant with PSD [17] and suggest changes within fronto-subcortical circuitries. However, the same neuropsychological pattern applies to elderly patients with endogenous depression, vascular depression or vascular dementia. The link between PSD and cognitive impairment could be even more distant if we consider that antidepressants might improve cognition independently from remission of depression [18].

Outcome and Mortality

Although several studies indicated that PSD affects functional recovery [5, 19], available data should be

interpreted cautiously [20] as the effect of antidepressants has not been evaluated in many studies.

Data fail to prove with sufficient evidence that improvement of the symptoms of depression improves the functional status [20]. However, direct patient reports might be more sensitive measures of stroke-related disability than standard measures. Patients with PSD have a threefold risk of mortality over the following 10 years in comparison to stroke patients without depression [5]. This risk seems independent of the cardiovascular risk, age, sex, social class, type of stroke or lesion location, but associates significantly with social isolation. PSD patients are also at increased risk of falling, and falling increases mortality. Early treatment of PSD may reduce the risk of mortality [21]. The suicide rate among stroke patients is low but not negligible (up to 7%) [22] and suicidal plans are frequent [23]. However, the prevalence of suicidal ideas seems similar between patients with stroke and patients with other chronic medical conditions [24]. Prestroke depression might be a risk factor for suicide in patients with PSD [25].

Treatment

PSD responds to pharmacological treatments [5] although the evidence is weak [26]. The recovery is considered significant when questionnaire scores reduce greater or equal to 50%, although this reduction might not correspond to disease remission. The natural or long-term course of the disease remains unclear.

Selective serotonin reuptake inhibitors (SSRIs) are the first-choice pharmacological treatment for a better tolerability profile. SSRIs have been shown to be more effective than placebo and tricyclic antidepressants but the effect of SSRIs on PSD has not been demonstrated unequivocally. There are no specific guidelines for the choice of drugs in the SSRI category. However, each SSRI has a specific pattern of inhibition of cytochrome-P450 isoforms and susceptibility to drug-drug interactions, which has to be taken in account. When efficacious, drug therapies should probably be protracted over 4–12 months. Low-dose methylphenidate seems highly and more rapidly effective than SSRIs in an high proportion of stroke patients [27, 28], a remarkable finding that should be further confirmed. It is a debated issue whether preventive treatment after stroke reduces PSD occurrence [29–31].

Cognitive, problem-solving, psychosocial-behavioral therapies and lifestyle interventions [32, 33] could be useful treatments, especially when all the factors contributing to depression are clearly assessed. Repetitive transcortical magnetic stimulation is promising [34, 35].

Poststroke Anxiety

DSM-IV-TR provides the actual diagnostic criteria of poststroke anxiety (PA). Most studies assessed generalized anxiety disorder but few data are available after stroke on panic attacks, agoraphobia, selective phobias and obsessive-compulsive disorders. The prevalence of PA remains high long term after stroke [36, 37] although probably slightly lower than PSD. However the two disorders co-occur very often [36].

PA shares many symptoms with the post-traumatic stress disorder. Both disorders follow a sudden and unpredictable life-threatening event. PA, as PSD, has certainly both biological and psychological foundations, but the relationship with stroke location remains unclear. Frontal-subcortical loops and limbic and paralimbic regions are probably involved. There is little information on the long-term outcome of PA and response to therapies. SSRIs are preferable as they have a better safety profile than benzodiazepines, especially on cognitive functions. Psychotherapy, cognitive behavioral therapy, relaxing techniques and psychosocial interventions are probably valid interventions.

Poststroke Mania

The DSM-IV classifies manic symptoms in the categories of: manic episodes, bipolar disorder, personality disorders (aggressive type) and impulse

control disorders. However, only manic episodes have been investigated in stroke. Symptoms of manic episodes are inflated self-esteem or grandiosity, decreased need for sleep, distraction, flight of ideas, and excessive involvement in pleasurable activities with potentially painful consequences. Nevertheless, manic symptoms are often also reported for stroke patients in terms of disinhibition syndrome, acquired sociopathy, pseudopsychopathic syndrome, and frontal lobe syndrome, terms that may engender confusion when comparing different studies. During the acute phase of stroke, manic behaviors generally emerge with strategic locations (frontal and temporal lobe, caudate nucleus, thalamus) within the right hemisphere, and are usually associated with significant memory disturbances, signs of the dysexecutive syndrome or spatial neglect [38, 39]. The prevalence of right hemispheral lesions in cases of poststroke mania could be interpreted in light of the motivational direction model or the approach-withdrawal concept (or fight-flight freezing system). These models postulate that the left and the right anterior region of the brain are part of two separate neural systems mediating motivation, respectively enhancing withdrawal or impulse toward action. Dysfunction of the right lateral anterior regions implies the loss of motivated withdrawal reactions to emotional stimuli and produces disinhibited behaviors. Indeed the dysfunction of the orbital-frontal system produces manic symptoms as a consequence of lack of affective empathy and rules of socialization. Most patients with poststroke mania have been treated with drugs frequently used for patients with primary mania (neuroleptics, anticonvulsants, and lithium). Poststroke mania is probably more difficult to treat because stroke patients are more prone to secondary effects of drugs.

Conclusions

Planning clinical studies for investigating poststroke mood disorders is encumbered by important methodological obstacles as many biological and non-biological variables are involved. These limits presumably explain why several studies on these disorders have not been replicated. Further advances in the knowledge of neurobiological factors may lead to new pharmacological therapies. The neuroscientific research should also focus on the linkage of neuropsychiatric poststroke disorders with specific brain dysfunction in terms of neural circuitries (in particular within fronto-subcortical functional systems) and of neurotransmitters or biochemical changes. New functional/structural biochemical and neuroradiological studies, assessment with new cognitive and emotional paradigms would be relevant for poststroke mood disorders in the future. However, the stroke patient is coping with a serious physical illness that reduces his or her self-integrity in terms of personal vulnerability and low self-esteem and generates high distress. Thus, for poststroke mood disorders behavioral or psychosocial interventions should also be extensively employed and assessed.

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Agnosia, Apraxia, Callosal Disconnection and Other Specific Cognitive Disorders

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Abstract

Cortical function deficits have long been studied by anatomoclinic correlations. Recent functional imaging studies have allowed scientists to better understand which cerebral areas and which networks are involved in cognitive function deficit. This chapter will review the current knowledge on agnosia, apraxia and callosal disconnection syndromes.

Agnosia

Agnosia is a neurological recognition deficit that affects a single modality not explained by loss of elementary sensory functions. Human processing of sensory information begins with a relay of sensory information from the sense organ to primary sensory cells in the cortex; the primary sensory areas receive direct input from extrapersonal space, then the information encoded in the primary regions is upstreamed to the same modality association areas for synthesis of initial perception. Agnosia can be distinguished as *aperceptive agnosia* where patients are not able to match identical stimuli: written words or pictures (visual), words and sounds (auditory) and objects (somesthesic) and as *associative agnosia* where patients will perform tasks normally in the modality being tested, but will not be able to match different stimuli; for example, the patient is not able to name the object seen, heard or touched (depending on the modality affected) but is able to name it through the unaffected modality [for recommended reading, see 1–12].

Types of Associative Agnosias

Visual Agnosias. The striate cortex, located in the upper and lower banks of the calcarine fissure, is the relay of visual information and its neurons are sensitive to color, form, texture and motion of objects. The striate cortex projects to the parastriate cortex that is surrounded by the visual associative area (peristriate cortex); the ventral associative area is specialized for color recognition, whereas the ventral associative area is sensitive to the visual perception of movements. Two divergent and parallel occipitofugal pathways emerge from the striate and parastriate cortex; the ventral fibers travel into the midtemporal and inferior lobe cortex carrying information about the visual attributes of objects, whereas the dorsal pathways convey more information on their spatial positions.

Lesions of the lower bank can lead to: (1) *Hemiachromatopsia:* loss of contralateral color perception due to lesion of the ventral associative area. When this area is intact but a lesion interrupts the fibers projecting to language

cortex, the patient suffers from *color anomia.* (2) *Prosopagnosia:* inability to recognize and name familiar human faces. Area specialized for face identification is located in the midportion of the fusiform gyrus. Here, facial recognition is not possible, whereas sex recognition, facial expression and age estimation are. (3) *Pure object agnosia:* global impairment of object recognition where patients are unable to name and understand the characteristics and the functions of visual objects. In this case, visual perception is normal and objects, when presented by another sensory modality, can be described.

Lesions of the upper bank can lead to: (1) *Asimultagnosia:* inability to perceive more than one object at a time. Patients report seeing things piecemeal and identify parts rather than the whole object. (2) *Akinetopsia:* inability to perceive visual motion. (3) *Optic ataxia:* visual motor disorder that impairs the reaching targets with the superior limbs and can afflict either one hand or both hands. The lesion responsible for this syndrome is localized in the superior parietal lobule, either unilateral or bilateral, with non-definite hemispheric differences. (4) *Environmental agnosia:* disorder of topographical orientation that impairs the capacity to locate a place and describe how to reach it. (5) *Apraxia of gaze:* impaired ability to direct visual fixation at desired target. (6) *Hemispatial visual neglect* [see chapter 16] and *dressing apraxia.*

Auditory Agnosias. Pitch and pure-tone discriminations are elaborated in the primary auditory cortex (A1). Damage of this area produces auditory perceptual impairment and cortical deafness. The auditory association areas are localized in the left temporal gyrus and respond to specific phonetic parameters of speech. The lesions of these areas result in *auditory agnosia* defined as the inability to understand environmental sounds and in *pure word deafness* defined as the inability to repeat or understand spoken language, despite good recognition of environmental sounds and no language deficit. *Phonagnosia* is the inability to recognize familiar voices and can result from damage of the ventral pathways in the associative areas; this is the auditory analogue of prosopagnosia.

Somatosensory Agnosias. S2 is involved in pain perception. In fact, S2 lesions can cause loss of pain perception and if these lesions are associated to damage of the insula and parietal operculum, patient can experience contralateral dysesthesia or pain asymbolia (no emotional response to pain). Somatosensory association areas are essential for touch localization, manual exploration, somatosensory coordination and encoding somatosensory memories; lesions of these areas can produce *hemispatial neglect, dressing apraxia* or *tactile agnosia.*

Anosognosia. This is defined as a disorder where patients do not perceive the presence or seriousness of sensory, perceptual, motor, affective or cognitive deficits. The term anosognosia is most frequently used to refer to only the unawareness of sensory-motor deficits following brain injury, but it has been reported that anosognosia can exist for hemiplegia, cortical blindness (Anton's syndrome), hemianopia, memory loss (amnesia), dementia and aphasia. Anosognosia is more common after right rather than left hemisphere stroke: reported frequencies in right hemisphere stroke range from 28 to 85%, and in left hemisphere stroke from 0 to 17%; a higher prevalence of anosognosia for hemiplegia has been reported in stroke patients with lesions with a mean diameter of 5 cm or greater. A meta-analysis of 23 studies has shown that the majority (56.2%) of patients with anosognosia had multiple lobe involvements. Neuroimaging studies have revealed the frequent involvement of prefrontal and parietotemporal cortical areas, as well as the thalamus, the right posterior insula and the medial and lateral parts of the pons.

Apraxia

Apraxia is defined as the inability to correctly perform skilled movements despite preserved motor and sensory systems, coordination, comprehension,

and cooperation. Praxis has long been considered a left hemisphere function, in fact apraxia occurs more frequently in patients with left versus right hemisphere injury. This disorder is usually bilateral. The network of structures underlying praxis is thought to include the frontal and parietal cortex, basal ganglia, and white matter tracts containing projections between these areas.

Studies have shown that apraxia negatively influences ADL functioning, gait, transfers and wheelchair mobility. Patients with apraxia typically present anosognosia of their deficits.

Ideational Apraxia. This is a severe apraxis disorder significantly affecting object use, characterized as a failure to carry out an ideational plan of a complex, multistep task (e.g. making a cup of tea). The distinguishing factor is that patients can obtain knowledge of how to perform a sequence task, but they fail to properly order the elements of the task, such as missing steps or doing steps out of order.

Ideomotor Apraxia. Ideomotor apraxia is the inability to correctly follow gesture pantomimes and imitations, whereas the automatic use of tools is less affected. The idea or plan of action is not impaired, but there are orientation, spatial and temporal errors in movements. Typical spatial errors include the positioning of hands in an appropriate posture, wrong orientation of a movement toward an imagined object, and failure to coordinate joint movements. Patients may also perform 'body part as object' errors by using a body part as if it were an imaginary tool. Nonetheless, patients are often able to perform the acts without difficulty in their daily lives; this phenomenon is called voluntary-automatic dissociation.

Limb-Kinetic Apraxia. Limb-kinetic apraxia is the inability to perform fine and precise finger movements, not related to elementary sensory-motor deficits (e.g. picking up a paperclip). Limb-kinetic apraxia differs from classical ideomotor apraxia because it tends to be independent of modality (e.g. verbal command vs. imitation) and typically there is no voluntary-automatic dissociation. This disorder has been associated with frontal lesions and can be difficult to differentiate from concurrent limb weakness.

Apraxia of Speech. Apraxia of speech is and articulatory disorder characterized by impaired coordination of sequential, articulatory movements necessary for producing speech. Articulatory errors and prosodic abnormalities are hallmarks of this disorder. Apraxia of speech differs from Broca's aphasia because the absence of truly linguistic deficits such as agrammatism or naming. This disorder differs from dysarthria as articulation is greater impaired than phonation. The brain regions that are usually associated to apraxia of speech include the left anterior insula, the left frontal cortex (frontal operculum) and the left basal ganglia.

Callosal Disconnection, Gerstmann's and Balint-Holmes' Syndromes

Callosal Disconnection Syndrome. Complete section of the corpus callosum results in two isolated hemispheres that are unable to carry out tasks coming from information processed in the other half of the brain. The typical findings of typical hemispheric disconnection due to total section of callosal commissure include: tactile anomia, ideomotor apraxia and agraphia of the left hand and constructional apraxia of the right hand. Other specific callosal syndromes include: (1) *'Alien hand' syndrome*: the patients are unable to recognize their left arm and hand without sensory loss. Usually this disorder is usually due to a lesion of posterior callosal commissure. (2) *Diagnostic dyspraxia*: abnormal motor behavior of the left hand dissociated from conscious will and activated by voluntary movements of the right hand. Left-hand movements can be antagonistic to the right actions, symmetric to the right actions and anticipatory to the right actions and occasionally patients are unable to voluntary left-hand movements. Typically, the

lesion responsible for this syndrome is localized on the posterior end of the corpus callosum. (3) *Autotopagnosia*: patients are unable to localize and name the parts of their own bodies. (4) *Alexia without agraphia:* involvement of corpus callosum splenium and left visual associative areas. The patients present right hemianopia and have problems in reading as visual perception of written language which is carried out in the right visual cortex is disconnected from the language area of the left hemisphere.

Gerstmann's Syndrome. This syndrome is characterized by a typical tetrad finger agnosia, left-right disorientation, agraphia and acalculia; the causative lesion is localized on the posterior-inferior parietal area.

Balint-Holmes' Syndrome. This is a severely disabling syndrome whose features include: optic ataxia, asimultagnosia (inability to perceive more than one object at a time), ocular apraxia (impaired gaze switch from one stimulus to another) and difficulty in perceiving distances and depth. Patients exhibit behavior likened to blind persons. Balint-Holmes' syndrome is due to bilateral lesions of the posterior parietal and occipital regions.

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Muscle, Peripheral Nerve and Autonomic Changes

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Abstract

Muscle, peripheral nerve and autonomic disorders associated with acute cerebrovascular events are a large spectrum of conditions, their pathophysiology, clinical features, frequencies of occurrence, prognosis and treatment are diverse; the disturbances may be primary or secondary to acute cerebrovascular events. These disorders have been previously defined as multiple neurological complications as the underlying pathophysiological mechanism may largely differ; their characterization may need a full clinical, neuroradiological, neurophysiological, immunological, biochemical and genetic analyses assessment, and an autonomic function test may also be needed as well as nerve and muscle biopsy. In this chapter we present multiple neurological complications secondary to acute cerbrovascular events.

Peripheral Nerve Changes after Stroke

Van Kuijk et al. [1] reported a decreased compound muscle action potential amplitude in the abductor digiti minimi muscle on the paretic side in the majority of a group of 27 post-stroke patients with no signs of motor recovery on average 1 week after the acute event and persisting in the subacute phase (3 weeks) in patients without motor recovery. Pathologic spontaneous activity (fibrillation potentials and positive sharp waves) was found on the hemiparetic side in 50% of 48 stroke patients, and it showed a significant correlation with the time after stroke onset, whereas no pathologic spontaneous activity was found beyond 6 months after stroke onset [2]. F-wave motor unit number estimate techniques showed fewer functional motor units already in the second week after stroke. Changes in peripheral nerve function on the paretic side could be attributable to many causes: altered metabolic environment, disuse, transsynaptic degeneration, ischemia, pressure effect, and decreased axoplasmic flow. Recently it has been observed that stroke patients have a higher rate of neuropathic involvement of the non-paretic limb as a possible consequence to exposure to vascular risk factors, such as altered triglyceridemia and hypertension that may play a role in the etiopathogenesis of cryptogenetic neuropathies [3].

Muscle Changes after Stroke

Hemiparetic stroke leads to various muscle abnormalities: combination of denervation, disuse, inflammation, remodeling and spasticity account for a complex pattern of muscle tissue phenotype change and atrophy. It has been observed that structural adaptive changes in muscle tissue start as early as 4 h after cerebral infarction, as a possible dysfunction of synaptic transmission of the muscle innervating motor neurons, leading to the reduction of motor unit numbers [4]. Interestingly, muscle weakness develops as well

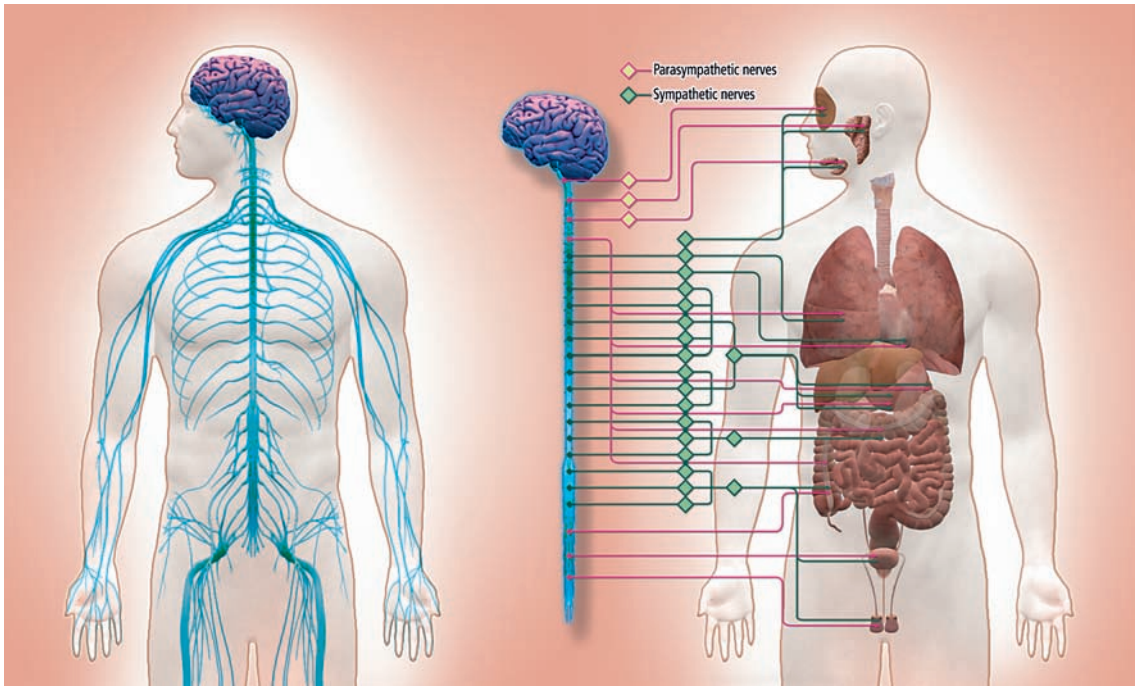

Fig. 1. Central and peripheral nervous system (left) and autonomic nervous system (right).

in the unaffected limb within 1 week after paretic stroke. Stroke causes the inversion of physiological muscle fiber shift, with an increase of fast-twitch MHC type II isoforms with more reliance on anaerobic metabolism [5]. The long-term muscle changes such as loss in muscle mass, reduction of cross-sectional area and increased intramuscular fat deposition occur between 3 weeks and 6 months in both paretic and non-paretic limbs.

Autonomic System Changes after Stroke

Disturbances of the autonomic nervous system are common in patients with various cerebrovascular diseases. They are attributed to damage of the central autonomic network, particularly in the frontoparietal cortical areas and in the brainstem, or to a disruption of the autonomic pathways descending from the hypothalamus via the mesencephalon, pons, and medulla to the spinal cord (fig. 1, 2).

Cardiovascular Regulation

Post-stroke ECG changes are quite frequent and do not necessarily reflect true morphologic myocardial damage, are quite frequent, they consist of prolonged QT intervals, depressed ST segments, flat or inverted T waves, and U waves, and occur in 60–70% of patients with intracerebral hemorrhage, in 40–70% of patients with subarachnoid hemorrhage, and in 15–40% of patients with ischemic stroke. These EKG abnormalities tend to appear later, reaching their maximum level during the first few days from the onset of the cerebrovascular symptoms, and often revert to normal within 2 weeks. Right hemispheric strokes are particularly associated with supraventricular tachycardia, and left hemispheric strokes with ventricular arrhythmias. Both systolic and diastolic blood pressures are transiently elevated immediately after stroke but resolve spontaneously after 7 days; in patients with supratentorial acute stage cerebral

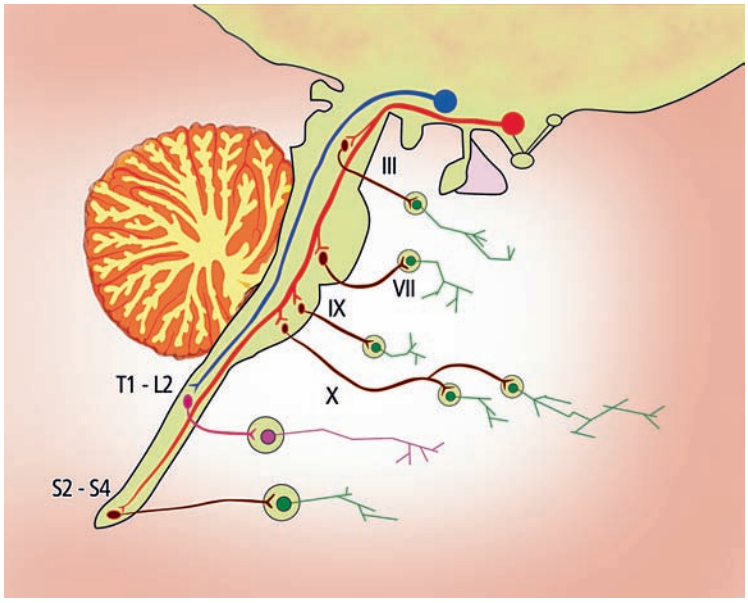

Fig. 2. Cranial parasympathetic and sympathetic nerves.

infarction this may be caused by a reduced parasympathetic regulation and relative increase in sympathetic output [6]. Baroreceptor reflex dysfunction, as a consequence of brainstem stroke, may cause blood pressure instability [7]. Heart rate variability may decrease as a result of cardiovascular autonomic dysregulation; heart rate suppression, involving all the spectral components of heart rate variability, such as high-frequency, low-frequency, and very-low-frequency power, seems to be persistent in hemispheric lesions, but it may be reversible in medullary brainstem lesions.

Thermoregulatory Dysfunction and Pain

Asymmetric sweating with cold hemiplegic limbs, reflecting changes in the sudomotor and vasomotor regulatory systems, are quite frequent after stroke. In a recent study [8] acute autonomic changes contralateral to the lesion, i.e. on the side of the deficit, were seen in 71% of all patients within the first week of a first-ever stroke, this included vasomotor changes such as edema (39%), increased skin temperature (56%), decreased skin temperature (7%), change in color (whitish 2%, red-bluish 8%) and pain (10%). In 10% of cases, pain and vasomotor changes did overlap. The authors observed that acute autonomic changes were significantly more frequent in the presence of lesions in the post-central cortex, insula, internal capsule, or basal ganglia and a negative association was seen for the brainstem. The 'complex regional pain syndrome' (CRPS) is a syndrome formed by the combination of pain, paresthesia, autonomic disturbances (such as trophic skin changes, edema, changes in temperature and skin color, and hyperhydrosis), and motor symptoms (tremor, dystonia, spasms, akinesia, or some degree of loss of motor coordination) in the late or chronic phase of stroke. Pain disproportionate in duration, severity, and distribution to what would be expected is the central symptom of CRPS, which is further subdivided into two syndromes: (a) CRPS I (or RSD), including regional spontaneous pain, sensory changes (e.g. allodynia or hyperalgesia), temperature abnormalities, abnormal sudomotor activity, vasomotor dysfunction (edema and abnormal

skin color and temperature), and trophic changes of nails, skin, and hair growth which occur after a noxious event such as stroke, and (b) CRPS II (causalgia), including all the above symptoms together with a peripheral nerve lesion. CRPS is more frequently encountered in spastic patients than in flaccid.

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Dysarthria and Mutism

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Abstract

Dysarthria is a speech disorder associated with impairments of intelligibility, smoothness, loudness, and clarity of articulations. Dysarthria involves disability of reproducing various physical, tonal, and sound features of speech sounds in oral speech; unintelligible and slurred articulation with swallowing of sounds is characteristic. Articulatory movements and speech are slow, patients complain to the sensations of a 'thick' tongue and 'porridge' in the mouth. Patients' phrases are constructed correctly, vocabulary is not affected, and the grammatical structure of words is preserved. Reading, writing, internal speech, and understanding of speech are unaffected. Several types of dysarthria have been described on the basis of the lesion locations. Dysarthria can be associated with lacunar syndromes as well. Mutism represents a condition when patient cannot speak and answer the questions, but remains conscious and is able to produce written speech.

Speech and language disturbances secondary to vascular lesions in subcortical white matter and basal ganglia are heterogeneous and can influence several aspects of voice, speech and language. These disorders are challenging because of a variety of cerebral structures and neurological circuits that are involved. Subcortical speech changes are often mild and transient, but can affect patients' professional and social activities and quality of life [1].

Dysarthria

Dysarthria is a speech disorder characterized by dysfunction in the initiation, control and coordination of the articulatory structures involved in speech output [2]. Dysarthria has been observed in 8–30% of all patients included in a number of large stroke series [3, 4] and may be the first and only clinical manifestation of cerebral ischemia.

For example, several lacunar syndromes, such as 'pure motor hemiparesis', 'ataxic hemiparesis', 'dysarthria-clumsy hand syndrome' and 'pure dysarthria' include dysarthria among the defining clinical characteristics. Dysarthria has been reported in 25% of patients with lacunar stroke and 30% of patients with stroke in the internal capsule [5]. Dysarthria describes a variety of speech disorders associated with disturbances of muscular control of the speech mechanisms due to damage of the central or peripheral nervous system. Dysarthria may result from impairment of any of the basic sensorimotor processes involved in the execution of speech, such as weakness, paralysis, incoordination, and sensory loss. The disabilities associated with various types of dysarthria can differentially disturb articulation, resonance, phonation, respiration, or prosody. Grewel [6] and Peacher [7] classified dysarthrias neuroanatomically on the basis of lesion topography. However, this classification does not consider interindividual variations of tract anatomy. Darley et al. [8]

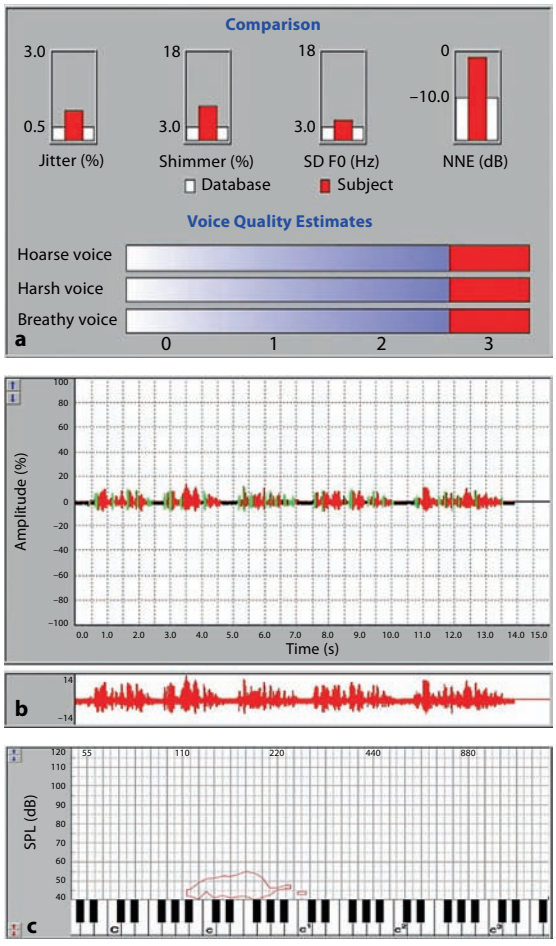

Fig. 1. Acoustic speech and voice analysis was done with Dr Speech 4 (Tiger DRS, Inc., USA) software, using modules for examination of (**a**) voice (vocal assessment), (**b**) speech (real analysis) and (**c**) speech profile (phonetogram).

suggested a classification of dysarthrias based on movement amplitude and tonus disturbances of the involved muscles (flaccid, spastic, ataxic, hypokinetic, hyperkinetic, and mixed) according to the listener's analysis of speech samples.

There is a paucity of new research on dysarthria. A Cochrane review updated in 2005 found that there are no published randomized controlled trials to support or refute the effectiveness of speech and language therapy for dysarthria following nonprogressive brain damage [9].

A prospective study of recovery from post-stroke dysarthria has recently been published [10]. Sixty-two consecutive patients with first-ever acute ischemic stroke and dysarthria without aphasia, dementia, anarthria or altered level of consciousness were evaluated by an experienced speech-language pathologist within 72 h after stroke onset. Thirty-eight of these patients were available for follow-up testing a minimum of 6 months later. Interestingly, only 7 of 38 patients (18%) complained of residual speech difficulties; thus, 82% of patients reported no ongoing difficulties with dysarthria 6 months post-stroke. Data from this study also indicated that 88.7% of noncerebellar strokes causing dysarthria were left-sided and that severity of dysarthria was worse with left-sided lesions.

Mutism

The term mutism is usually defined as complete loss of speech in a conscious subject with no organic lesion of the neuraxis (functional forms), or more rarely with organic lesions of the neuraxis (organic forms).The functional forms are mostly in the area of the psychiatrist (psychosis, autism). The organic forms are subdivided into six types, according to the area of the nervous system affected: (a) lesion of Broca's area (motor aphasia), (b) lesion of the supplementary motor area of the dominant hemisphere, (c) lesion of the mesencephalic reticular formation (akinetic mutism), (d) stereotactic lesion such as those following post-bilateral thalamotomy in parkinsonian patients, (e) diffuse bilateral hemispheric lesions (pseudobulbar palsy), and (f) bilateral pharyngeal or vocal cord paralysis (peripheral nerve palsy). Cerebellar mutism is yet another organic form. Patients with cerebellar mutism usually recover their speech within 1–6 months [11].

The ischemic stroke origins of mutism are often difficult to assess at the acute stage. Accordingly, the search for the underlying mechanism as the

localization of the damages may be difficult by conventional radiological techniques. Diffusion-weighted MRI may accurately identify patients with acute ischemic stroke and distinguish them from those who mimic acute stroke better than clinical and conventional neuroradiological methods [12].

Aside neuroimaging methods, neurolinguistic and acoustic analysis (Dr Speech 4; Tiger DRS, Inc., USA) in patients with ischemic subcortical lesions can provide valuable information for understanding mechanisms of language and speech and their disturbances, and assisting in planning patient management [1].

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Dysphagia – Pathophysiology, Diagnosis and Treatment

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Abstract

Dysphagia is an extremely common disorder after stroke, affecting as many as half of acute stroke sufferers. It is associated with respiratory complications, increased risk of aspiration pneumonia, nutritional compromise and dehydration, and detracts from quality of life. For this reason, dysphagia significantly affects outcome and is associated with increased morbidity and mortality. Formal dysphagia screening protocols significantly reduce the rate of pneumonia and improve general outcome. Furthermore, early behavioral swallowing interventions are associated with a more favorable outcome in dysphagic stroke patients. This chapter reviews the pathophysiology of swallowing dysfunction, and the diagnosis and treatment of patients with dysphagia after an acute stroke.

Pathophysiology

Dysphagia is a common functional impairment of acute stroke, affecting as many as half of all patients [1]. The true incidence of dysphagia after acute stroke is unclear, but estimates range from 20 to 90%, depending on the timing of the assessment, diagnostic methods and criteria [2]. Swallowing dysfunction generally resolves in about half of stroke patients within 7 days, and only 11–13% of patients have a persistent swallowing dysfunction after 6 months [3].

Dysphagia is associated with a higher incidence of medical complications and increased overall mortality. The main reason for the higher morbidity and mortality is aspiration pneumonia. There is an increased risk of pneumonia in patients with dysphagia and an even greater risk in patients with aspiration. There is also increasing evidence that dysphagia contributes significantly to protein-energy malnutrition, dehydration and increased length of hospital stay, all of which increase healthcare expenditure [4].

Although dysphagia is commonly observed in acute stroke patients, the neural control of swallowing remains unclear. Swallowing is a complex function, with both voluntary and reflexive components. Five cranial nerves and more than 50 muscles in the head and neck are involved in oropharyngeal swallowing. Both brainstem and cortical areas are involved in the neural processing of swallowing. Daniels and Foundas [5] have developed an anatomic model of swallowing defined as a distributed neural network involving bilateral input from the sensorimotor cortex with descending input to the brainstem medullary swallowing center.

Dysphagia has traditionally been associated with brainstem and bilateral cerebral infarction, though it has more recently been shown to occur

in isolated cerebral infarctions as well. Functional and anatomic imaging studies have identified several sites that play an important role in swallowing, including the primary sensorimotor cortex, insula, anterior cingulate, internal capsule, basal ganglia and thalamus.

Evaluation of Dysphagia

Early assessment and management of dysphagia significantly reduce the rate of pneumonia and improve the overall outcome after stroke [6]. An interdisciplinary team's involvement in the dysphagia evaluation process is crucial to address the complex needs of dysphagic individuals. The team should include a physician, speech-language pathologist, dietician, occupational therapist and nurse, as well as other subspecialty experts, if required. A comprehensive assessment of swallowing function after stroke begins with a thorough medical history and examination of the lower cranial nerves. A clear description of dysphagia-related symptoms, such as choking or coughing with food or liquid, vomiting or the sensation of food stuck in the throat, provides information regarding possible deficits and the need for further evaluations.

Clinical Swallowing Evaluation

Given the high prevalence of dysphagia and its complications, a swallowing screening examination should be completed as part of every stroke patient's initial assessment. Elements commonly evaluated at the bedside screening are consciousness level (altered alertness or arousal) postural control, difficulty in managing oral secretions and weak voluntary cough. The goals of the swallowing screening examination are to detect possible signs of dysphagia and aspiration and identify patients in need of further evaluation. The water swallow test is commonly used as a screening tool. The patient drinks a predetermined amount of water (usually about 100 ml) without pausing while clinicians see whether there are any signs of aspiration or dysphagia, such as no laryngeal elevation, coughing, choking and wet or 'gurgly' vocal quality. The results of this screening should be interpreted with caution as they (a) have limited predictive ability, (b) cannot detect silent aspiration, (c) cannot be used to determine whether other forms of food/liquid are safe, and (d) cannot provide information regarding the mechanism of dysphagia. If the screening examination suggests that dysphagia is present or if the patient complains of symptoms associated with swallowing dysfunction, a thorough clinical swallowing evaluation (CSE) is required. The CSE examines an individual's potential risk for dysphagia with various food and liquid consistencies and is usually performed by a speech-language pathologist. During a CSE, clinicians conduct a thorough oral, pharyngeal and laryngeal motor and sensory assessment. Liquids and solid foods are presented. Oral function is observed to ensure that substances can be managed with adequate lip, tongue and jaw control and movement. The timing and strength of pharyngeal swallowing is assessed through palpation of the tongue base, hyoid bone and larynx. Clinicians look for signs of overt aspiration before, during and after swallowing. While silent aspiration cannot be reliably detected during a bedside examination, several clinical signs are associated with the risk of aspiration. These include dysphonia, dysarthria, weak cough, abnormal laryngeal elevation, impaired control of secretions, and cough or voice change after swallowing. Decline in pulse oximetry during swallowing has been explored as a potential tool to predict aspiration, though results have been contradictory [7, 8]. An instrumental examination of swallowing is essential to fully assess patients with clinical signs of dysphagia or who are at high risk of silent aspiration.

Instrumental Swallowing Evaluation

Videofluoroscopic Swallowing Study (VFSS). The VFSS is the gold standard for evaluating swallowing disorders. The patient is tested in an upright

position to recreate normal eating and drinking conditions. During VFSS, the patient eats and drinks a variety of solids and liquids mixed with barium while images are recorded by means of videofluorography. The purpose of this test is to identify the structural or functional abnormalities related to swallowing and to identify circumstances for safe swallowing. These include oral bolus control and propulsion, pharyngeal transport, timing and coordination of swallowing, presence and depth of laryngeal penetration or aspiration. The VFSS also offers the opportunity to test compensatory maneuvers, such as modifications in posture or bolus characteristics that may improve the safety and efficiency of swallowing. A VFSS is contraindicated if the patient has a low level of consciousness or is unable to cooperate or follow commands.

Fiberoptic Endoscopic Evaluation of Swallowing (FEES). If a VFSS cannot be performed, the FEES can be used to visualize the anatomy of the pharynx and larynx and vocal fold function during eating without X-ray exposure. The FEES is a bedside procedure in which a nasally inserted flexible endoscope is used to directly view the nasopharynx and larynx during swallowing. It is also highly sensitive to silent aspiration, though it does not visualize essential aspects of swallowing, such as the oral and esophageal stage of swallowing, or critical events of pharyngeal swallowing, including opening of the upper esophageal sphincter, elevation of the larynx or contraction of the pharynx.

Treatment of Dysphagia

The management of dysphagia in stroke patients has the following general goals: to prevent aspiration, improve the ability to eat and drink, and ensure good nutrition. A fundamental principle of rehabilitation is that the best therapy for any activity is the activity itself; as swallowing may consequently be considered the best therapy for swallowing disorders, rehabilitation should be aimed at identifying ways of ensuring safe and effective swallowing in individual patients.

When safe feeding is not possible, a pharyngeal bypass measured may be employed to eliminate the need for oropharyngeal swallowing and provide nutrition and hydration. Short-term feeding can be accomplished via a nasogastric tube. Nasogastric tubes have risks and can result in numerous complications, including reflux aspiration, improper positioning, dislodgement and ulceration of pharyngeal and esophageal tissue. Long-term feeding options include percutaneous gastrostomy tubes. The use of a nasogastric tube or percutaneous gastrostomy are both effective for early nutrition; the latter method is associated with fewer tube failures and possibly a lower risk of aspiration pneumonia.

Current treatment for dysphagia includes prevention of aspiration in the form of diet and fluid modifications, compensatory maneuvers, position changes and rehabilitation exercises. Diet modification is a common treatment for dysphagia. Modifications in food consistency are individually determined by means of the CSE and VFSS. In general, thin liquids are the most difficult to control and are more likely to be aspired because they can leak into the pharynx before swallowing is triggered. Hence, thickened liquids and soft cohesive solids are generally those with the safest consistency. By increasing the viscosity or thickness of the food or liquids bolus in patients with oral sensory or motor deficits, the material is less likely to escape from the oral cavity, fall into the laryngeal inlet or penetrate the incompletely sealed larynx during the delay before pharyngeal swallowing starts. In addition to changes in diet, maintenance of oral feeding often requires compensatory techniques to reduce aspiration or to improve pharyngeal clearance. A variety of behavioral techniques are used, including modifications in posture, head position and respiration, as well as specific swallowing maneuvers.

Oral sensory stimulation, involving altered temperature and taste, may be considered as a

therapy because it can alter the timing of swallowing by reducing both the oral onset time and pharyngeal delay time. Therapeutic exercises are used to improve the patient's oral motor range of motion, strength and coordination of oral, pharyngeal and respiratory muscles for swallowing. There are no specific pharmacological treatments for oral or pharyngeal dysphagia, though some symptoms may be managed with medication. Anticholinergic drugs and botulin toxin injections can reduce salivary flow in individuals with sialorrhea and chronic aspiration of oral secretions.

Neuromuscular electrical stimulation (NMSE) is a relatively new treatment for oropharyngeal dysphagia [9]. It involves passing a small electrical current transcutaneously via electrodes to stimulate the neuromuscular junction and create a muscle contraction. NMES for dysphagia entails applying electrodes to the muscles of the head and neck, and stimulating those muscles that are weakened or hemiparetic by means of electric pulses. This is generally combined with the subject swallowing food or fluids that are predetermined to represent the most appropriate consistency that the person can tolerate without aspiration. NMSE is believed to contract the muscles used for swallowing, thereby improving swallowing function. Further research on the effects of NMES is warranted before surface electrical stimulation can be recommended as treatment of dysphagia.

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Ventilatory Disorders

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Abstract

Breathing is a primal homeostatic neural process, regulating levels of oxygen and carbon dioxide in blood and tissues, which are crucial for life. Rhythmic respiratory movements must occur continuously throughout life and originate from neural activity generated by specially organized macro- and microcircuits in the brainstem. In the respiratory network there is a spatial and dynamic hierarchy of interacting circuits, each of which controls different aspects of respiratory rhythm generation and pattern formation, which can be revealed as the network is progressively reduced. The motor pattern during normal breathing is considered to consist of three phases: inspiration, post-inspiration and expiration. The expression of each rhythmogenic mechanism is state-dependent and produces specific motor patterns likely to underpin distinct motor behaviors. Vascular neurological disorders affecting these areas or the respiratory motor unit may lead to impaired respiratory activity. Manifestations associated with disorders of this network include sleep apnea and dysrhythmic breathing frequently associated with disturbances of cardiovagal and sympathetic vasomotor control. Respiratory dysfunction constitutes an early and relatively major manifestation of vascular neurologic disorders; ventilation control and breathing behavior correction are necessary to improve stroke management.

Control of ventilation depends on a brainstem neuronal network that contains neurons critical for respiratory rhythmogenesis and controls activity of the motor neurons which innervate the respiratory muscles. This network includes the pontine respiratory group (PRG) and the dorsal respiratory group (DRG) and ventral respiratory group (VRG) in the medulla [1]. Respiratory rhythm depends on the coordinated firing of inspiratory, post-inspiratory and expiratory neurons [2]. Coordinated activity of respiratory neurons is important not only for breathing and ventilation but also for vocalization, swallowing, coughing and vomiting. Impaired respiratory activity (IRA) is frequent in cerebrovascular disease (CVD). Reduced or abnormal ventilatory function is a predictor of mortality due to CVD [3].

Physiology and Pathophysiology of Respiration Control

Breathing is controlled by voluntary (behavioral) and automatic (metabolic) mechanisms that are governed by different although integrated neuronal systems. Voluntary respiration is assured by the cortex and the corticospinal system, whereas automatic respiration depends on hierarchically organized structures in the brainstem that are modulated by supratentorial influences. Neural circuits controlling breathing are organized within serially arrayed and functionally interacting brainstem compartments extending from the

pons to the lower medulla [4]. The core circuit components that constitute the neural machinery for generating respiratory rhythm and shaping inspiratory and expiratory motor patterns are distributed among three adjacent structural compartments in the ventrolateral medulla. This network comprises three groups of interconnected neurons: PRG, DRG, and VRG [2].

The PRG areas have several functions in the control of respiration, including respiratory phase timing and integration of reflexes initiated by pulmonary mechanoreceptors. The parabrachial nucleus also transmits information from medullary respiratory neurons to the amygdala, hypothalamus and other suprapontine structures. The DRG located in the nucleus of the solitary tract (NTS) is the first central relay station for afferents from peripheral respiratory chemo- and mechanoreceptors. The VRG consists of a bilateral longitudinal column of neurons located in the ventrolateral medulla and extending from the cervical cord C1 level to just below the facial nucleus. The most rostral portion of the VRG includes the Bötzinger complex, which contains expiratory neurons that inhibit the inspiratory neurons of the VRG and project to the spinal cord. The pre-Bötzinger complex consists of propriobulbar neurons that play a critical role in respiratory rhythm generation. These neurons are identified by the presence of neurokinin-1 receptors for substance P. Immediately caudal to the pre-Bötzinger complex is the rostral VRG located ventral to the nucleus ambiguous and containing inspiratory bulbospinal neurons. The most caudal portion of the VRG corresponds to the nucleus retroambigualis and extends from the obex to C1 on the spinal cord and contains bulbospinal expiratory neurons that project to the intercostal and abdominal motor neurons. Suprapontine structures, including the cerebral cortex, hypothalamus, amygdala and periaqueductal gray matter of the midbrain play a major role in normal respiratory control during speech, locomotion, and response to stressors including the defense reaction as shown in experimental studies.

These neurons are part of a central pattern generator network that controls the periodic activity of bulbar and spinal motor neurons innervating the respiratory muscles. The generation and maintenance of normal respiratory rhythm and ventilation requires a tonic 'drive', which in turn maintains respiratory neuron excitability. This drive can arise from arousal systems or central and peripheral chemoreceptors sensitive to changes in PaO_2, $PaCO_2$ or both, and from inputs from respiratory mechanoreceptor afferents (metabolic mechanisms). In many cases, these lesions lead to dysfunction not only of respiratory but also of cardiovascular control systems.

Clinical Manifestations of Impaired Automatic Control of Ventilation

Considering the complexity of breathing control anatomy and physiology, focal vascular brain lesions impair breathing in different ways according to the extension and topography of the lesion. Respiratory function during wakefulness and/or sleep have been reported in patients with CVD (table 1) [5]. Vascular lesions affecting the PRG, NTS, VRG or the central chemoreceptors may manifest with central alveolar hypoventilation (Ondine's curse), abnormal respiratory rhythm, or both. The posterior inferior cerebellar artery and the vertebral artery, or branches of these arteries, are responsible of vascular brainstem respiratory injury. The types of respiratory rate and pattern abnormalities in acute stroke infarction are not specifically related to the level of lesions, but rather to the size and bilaterality of the lesions.

Bilateral medullary infarctions resulting in destruction of the pyramids impair voluntary, but not automatic, control of respiration. Those affecting the medullary tegmentum produce failure of automatic breathing, impaired ventilatory responses to CO_2, and sleep apnea but spare voluntary breathing during wakefulness [6]. Even unilateral lesions of the ventrolateral medullary tegmentum involving the NTS, VRG and their connections,

Table 1. Abnormal breathing in brainstem and hemispheric stroke: various respiratory patterns

Breathing type	Definition
Apnea/hypopnea	A cessation of oronasal airflow ≥10 s, hypopnea by a reduction of oronasal airflow ≥10 s by ≥50%, or ≥30% when associated with an oxygen desaturation ≥4%
Apneustic breathing	Deep, prolonged inspiration, with an inability to expire, lasting seconds, followed by overinspiration and then rapid gasping hyperventilation before returning to a more normal respiratory rate and rhythm
Central alveolar hypoventilation (Ondine's curse)	Abnormal respiratory rhythm
Central periodic breathing (CPB)	A number of irregular inspirations followed by apnoeic periods
Central periodic breathing during sleep (CPBS)	As ≥3 cycles of regular crescendo-decrescendo breathing associated with reduction of ≥50% in nasal airflow and respiratory effort lasting ≥10 s
Central sleep apnea (CSA)	Repetitive cessations in air flow due to changes in respiratory drive
Cheyne-Stokes respiration (CSR)	Periods of hyperpnea regularly alternating with periods of apnea
Cheyne-Stokes variant (CSV)	Phasic variations in depth of respiration without definite apneic periods occurred
Cluster respiration	Several breaths of varying depth interspersed with apneic episodes, usually of irregular length
Fixed breathing	Inability to initiate any kind of volitional respiratory movement
Obstructive sleep apnea (OSA)	Repetitive cessations in air flow due to physical airway obstruction
Ratchet breathing	Irregular and jerky inspiratory breaths with short apneic pauses during mid-inspiration
Sleep-disordered breathing (SDB)	Wide spectrum of sleep-related respiratory abnormalities ranging from snoring to upper airway resistance syndrome to sleep apnea, including obstructive, central and mixed forms
Tachypnea (T)	Rapid, regular respiratory rates >30 per min

or both, may produce impaired automatic ventilation and sleep apnea and may occasionally also affect voluntary respiration even with complete sparing of the corticospinal tracts [7]. Unilateral lesions of the lateral medulla, including the VRG, as occurs in the Wallenberg syndrome, lead to blunting of the ventilatory response to CO_2 [8]; lateral medullary infarcts may also lead to sleep apnea syndrome, particularly when there are other predisposing factors such as a long uvula or nasal septum deviation. Cheyne-Stokes respiration (CSR), which typically accompanies bilateral infarcts of the cerebral hemispheres, also occurs in ischemic stroke involving the brainstem [9]. CSR is a form of periodic breathing which was observed after bilateral hemispheric or upper brainstem infarction, and was recognized as a sign of impending brainstem herniation [10]. Reciprocally, poor respiratory function appears to increase the risk of ischemic damage to the brain. White matter lesions and lacunar infarcts in elderly patients may be related to impaired respiratory function [11].

Respiratory alkalosis is present in varying degrees in most patients with either tachypnea or prominent CSR. The syndrome of central alveolar hypoventilation (Ondine's curse) includes repetitive

morning headaches, nocturnal sleep disruption, or daytime tiredness and sleepiness. Cyanosis, irregular breathing patterns during sleep or wakefulness, or absence dyspnea during exercise may occur. Diagnosis is confirmed by demonstrating an abnormal ventilatory response to provoked hypercapnia, with normal or near-normal response to hypoxia in the absence of infectious, cardiac, pulmonary, and neuromuscular causes. Sleep-disordered breathing (SDB) is common in patients during acute phase after stroke onset and appears to be associated with a worse functional outcome during the early recovery period following stroke, increasing the likelihood of dependency [12]. Sleep-induced apnea and disordered breathing refers to intermittent, cyclical cessations or reductions of airflow, with or without obstructions of the upper airway (OSA). An association between OSA and stroke has been observed in numerous cross-sectional studies [13], however in most cases it was not possible to determine whether OSA preceded the onset of stroke and thus could be involved in pathogenesis.

In the acute phase the assessment of breathing in stroke patients should include recordings made while the patients are sleeping as well as monitoring of both breathing effort and nasal/oral airflow. A mechanical ventilatory correction in selected acute stroke patients might have a beneficial effect on brain perfusion. Ischemic penumbra may be present for many hours and early non-invasive ventilatory correction may be justified. This is a novel therapeutic target and the missing link in the pathogenesis of early ischemia and stroke recurrence.

Conclusion

The IRA is a common disorder associated with CVD and worst outcome. Early monitoring and IRA correction are necessary to improve stroke management. Further studies are needed to assess the clinical significance of IRA with respect to treatment and outcome of acute stroke patients.

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Lacunar versus Non-Lacunar Syndromes

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Abstract

Small-vessel disease is the accepted most frequent cause of lacunar stroke. The main clinical features seen with lacunar infarcts are motor and/or sensitive deficit, ataxic sign, without cortical involvement. A lacunar syndrome is generally the result of a small deep infarct within the territory of a single perforating artery with the maximum diameter on imaging of 15 mm. Recent studies have demonstrated alternative causes of lacunar stroke other than small-vessel disease (e.g. cardioembolism, atherosclerosis or other causes), especially in large lacunae, with a potential relevance on functional outcome. These findings suggest that lacunar stroke is not always a benign disease. Moreover, clinical features may be significant in terms of disability in lacunae in close proximity to crucial anatomical site. The following chapter reports the classical lacunar syndrome and discusses the debated etiology of lacunar stroke.

In 1991, the Oxfordshire Community Stroke Project (OCSP) proposed four defined subgroups of cerebral infarction in which lacunar infarcts (LACI) [1] was defined as infarct confined to the territory of the deep perforating arteries. These definitions, based exclusively on presenting symptoms and signs, have been estimated as being easy to apply, have a good interobserver reliability, have the ability to predict the prognosis, and have good correspondence to the underlying pattern of vascular origin and cranial CT [2]. Later the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) in 1993 developed a new system to classify the subtypes of ischemic stroke: large-artery atherosclerosis, cardioembolism, small-vessel occlusion, stroke of other determined etiology, and stroke of undetermined etiology. The classification system is based on the clinical/neuroimaging result and also on ancillary feature studies with the possibility to apply the classification in clinical trials that recruit patients with acute ischemic stroke. The diagnosis of small-vessel occlusion was limited to cases with one of the traditional lacunar syndromes with no evidence of cerebral cortical dysfunction and who have a brain lesion <15 mm in diameter on imaging. Also a history of diabetes mellitus or hypertension supports the clinical diagnosis [3]. However, the same author found that the risk factor profile and some of the clinical symptoms of the lacunar syndromes overlap with those of large-artery atherosclerosis, opening the debate on lacunar stroke. Since Fisher's first observation [4], lacunae were defined as the result of occlusion of a single perforating artery, and lacunar infarcts were divided into large (15–20 mm in diameter) and very small (3–4 mm) suggesting that the large lacunae were often symptomatic whereas the very small lacunae tended to be asymptomatic, unless strategically located in a sensory or motor tract [5].

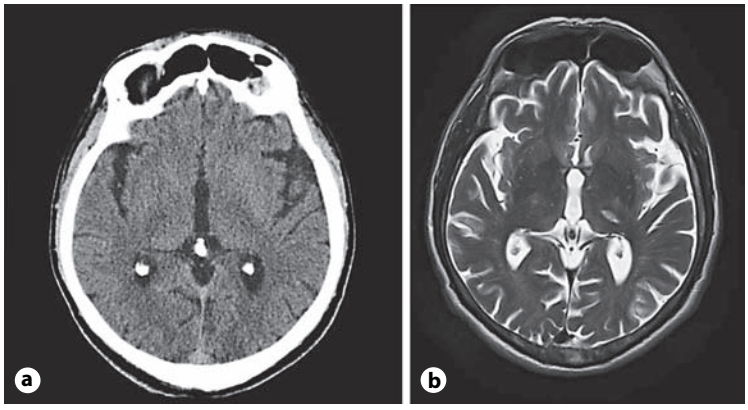

Fig. 1. **a**, **b** Thalamic lacunae detected on MRI in a patient with negative CT.

Clinical Features

Pure Motor Stroke (PMS). Patients presenting a pure motor hemiparesis often have a lesion in an area where motor fibers are close together (e.g. basal ganglia, pons) which receive their vascular supply by deep perforating 'end' arteries, isolated occlusion of which will result in an ischemic lacuna [6]. Other authors found that basilar artery branch disease was the most common etiology of PMS in pontine infarct due to stenosis or occlusion of basilar artery [7, 8]. PMS is generally considered to be the commonest lacunar syndrome in clinical practice – 46% in the OCSP, 57% in the Stroke Data Bank (SDB) and 45% in the Northern Manhattan Stroke Study (NMSS) [9–11]. Pure motor hemiparesis has been described secondary to infarct in the anterior limb of internal capsule with a prevalent faciobrachial weakness [12]. Lacunae located more posteriorly in the capsule seem likely to produce a greater deficit in the leg than in the arm, whereas a monoparesis with prevalent distal upper limb involvement may be caused by pontine infarct [13]. In a hospitalized stroke population a pure motor hemiparesis was found in 53.1% of patients and the corona radiata/centrum semiovale were the most frequent sites involved [14]. In the recent years, several anatomical sites have been identified thanks to a deeper assessment (fig. 1) possible with the increased use of techniques such as magnetic resonance imaging (MRI).

Pure Sensory Stroke (PSS). Most authors agree that the lesions causing PSS are the smallest of the symptomatic deep infarcts [10, 15] and the anatomical sites more often involved could be the thalamus or the anterior thalamic radiation; moreover, PSS has been reported with a lesion in the anterior limb of the internal capsule [6]. A PSS is not a common cause of lacunar syndrome in clinical practice – 6% in the OCSP, 7% in both the SDB and NMSS [9–11]. Occasionally a PSS could be the result of lesions located in the lateral pontine tegmentum, involving the medial lemniscus and the lateral spinothalamic tracts in the rostral pons [16]. A recent study reported the possibility to find PSS in 9.5% of patients with lacunar syndrome not due to lacunar infarcts [17].

Ataxic Hemiparesis (AH), Homolateral Ataxia and Crural Paresis (HACP) and Dysarthria-Clumsy Hand Syndrome (DCHS). The concept of ataxia and motor deficit was first described by Fisher and Cole [18] in 1965 who reported a case of HACP in a patient with lower limb weakness, a Babinski sign and striking dysmetria of the arm and leg of the same side probably due to a lacuna in the posterior limb of internal capsule. DCHS was described originally by the same author as being 'chiefly of dysarthria and clumsiness of one hand' as the result of pontine lacunae [19]. Patients with DCHS were found to have pontine infarctions contralateral to the symptomatic side

in a more recent MRI study [20]. In the largest study on AH, infarcts were demonstrated more frequently in the internal capsule (39%), followed by thalamus (13%), corona radiata (13%), lentiform nucleus (8%), cerebellum (4%) and frontal cortex (4%) [21], rather than in the basis pontis as described in the original clinicopathological work. An AH is currently defined by the association of hemiparesis or corticospinal signs (weakness or hyperreflexia, Babinski's sign) with an ipsilateral cerebellar incoordination. These features have usually been explained by a lesion in the white matter, involving both the corticospinal and cerebello-thalamo-cortico-ponto-cerebellar tracts [22], but it has also been found to involve the thalamus or cortical area. Some authors proposed that partial hemiparesis, nystagmus, and dysarthria are suggestive of an infratentorial lesion [23], whereas facial sparing and lack of dysarthria and paraesthesia would be associated with a hemispherical lesion [24, 25]. In the thalamic infarction, contiguous involvement of the internal capsule due to ischemia or edema may explain corticospinal signs, whereas pain and ataxic disturbances were related to involvement of the thalamus itself and caused the so-called 'painful ataxic hemiparesis' [26]. Indeed, thalamic lesions could be associated with a wide series of clinical findings. Recently the author reported small-vessel infarctions producing AH in 3 cases who presented with left-sided AH and small right frontal subcortical white matter infarcts on MRI and the evidence on SPECT of decreased metabolism in the contralateral cerebellar hemisphere, indicative of crossed cerebellar diaschisis [27]. AH accounted for 9% of all LACS in the OCPS, AH for 10% and DCHS for 6% in SDB, and in the NMSS, 18% of LACS were AH [9–11].

Sensorimotor Stroke (SMS). The original report of SMS in 1965 was by Fisher and Curry [22] who described a case of PMS with symptoms (but no signs) of sensory loss. Later a single case of SMS with severe hemiparesis was reported, which progressed to total paralysis and then gradually improved, and the sensory and postmortem findings demonstrated lacunae in the ventral posterior nucleus of the thalamus but there was also pallor of the adjacent capsule [28]. Other authors found that lacunae can cause a sensorimotor stroke with a prevalent site involved in the thalamocapsular-corona radiata region or the adjacent putamen [29]. Furthermore, in the rolandic cortex, the close anatomic and vascular rapport between motor and sensory areas makes SMS possible due to cortical infarction anterior to the rolandic fissure [30]. In the SBD, 31% of patients had a lesion in the posterior of the internal capsule, 22% in the corona radiata, 7% in the genu of the capsule, 6% in the anterior limb of the capsule, and 9% in the thalamus [10].

Pathogenesis and Outcome

Hypertensive small cerebral vessel disease is still the most frequent cause of lacunar stroke whereas cardiac emboli, embolism from artery-to-artery atheroma or intracranial stenosis are considered uncommon causes of lacunar stroke [31, 32]. Data from recent studies suggest that the detection on MRI of multiple acute brain infarcts in patients with lacunar stroke should be followed by an intensive search for a stroke mechanism other than small-artery disease [33]. The problem in lacunar stroke is the assigning etiology, since an atheromatous branch disease and lipohyalinosis could coexist with a cardiac and intra-arterial source of emboli [34] making it difficult to distinguish if cardioembolism or severe carotid stenosis are causal or simply co-pathologies. In a consecutive stroke population, 27% of the lacunar strokes could be ascribed to a different etiology than small-vessel disease [14]. Although lacunar stroke has been associated with a good outcome in prior studies [35, 36], data correlating the etiology of lacunar stroke and long-term follow-up are still debated. Patients with multiple etiologies had a poorer outcome and the neurological deficit at presentation is related to a worse outcome in patients with

lacunar stroke due to non-small-vessel disease compared with lacunar stroke due to small-artery disease [37]. The prognosis of lacunar stroke does not seem to be always benign as 30% of patients remain dependent [1, 38] and long-term studies report that up to 25% of patients have a second stroke within 5 years [39]. Sacco et al. [40] in a population study on lacunar stroke found an annual mortality rate of 13.0% and an annual recurrence rate of 2.8%; in a hospital-based study the annual mortality rate was 4.4% and the annual recurrence rate 9.9% [14]. These findings indicate that lacunar stroke is not always a benign disease and support the clinical utility of further investigations to stratify lacunar strokes in different risk categories for an adverse outcome.

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Arterial Territories of the Human Brain

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Abstract

We present a brain map of the areas supplied by various arteries in the brainstem, cerebellum and cerebral hemispheres. Arterial territories are depicted in a form that is directly applicable to neuroimaging slices in clinical practice. The arterial territories are outlined based on an extensive overview of anatomical studies of cerebral blood supply. For arterial territories of the hemispheres, we present the variability of the cortical territories of the three main cerebral arteries and define the minimal and maximal cortical supply areas.

In this chapter, we present a brain map of the areas supplied by various arteries in the brainstem, cerebellum and cerebral hemispheres. Arterial territories are depicted in a form that is directly applicable to neuroimaging slices in clinical practice. The map is presented on a series of 24 templates, based on a bicommissural plane passing through the center of the anterior and posterior commissures. The sections of the brainstem and cerebellum (sections I–XII) are 4 mm thick, whereas those of the cerebral hemispheres (sections XIII–XXIV) are 8 mm thick. The anatomical structures are shown on the right side of the sections and the arterial territories appear on the left.

Morphological data for the 24 sections are based on anatomical atlases by Duvernoy [1–3]. The arterial territories are outlined based on an extensive overview of anatomical studies of cerebral blood supply. This overview included either vascular injection studies or microanatomic studies of the cerebral arteries, and is developed in more detail elsewhere [4–6]. For arterial territories of the hemispheres, we have chosen to explain in detail the variability of the cortical territories of the three main cerebral arteries and to define the minimal and maximal cortical supply areas with reference to a baseline anatomical study [7].

This chapter is intended to provide a graphical overview of the anatomy of the cerebral arteries. A more detailed approach can be found elsewhere [8].

Arterial Supply of the Brainstem

Arterial trunks supplying the brainstem include the vertebral artery, basilar artery, anterior and posterior spinal arteries, posterior inferior cerebellar artery, anterior inferior cerebellar artery, superior cerebellar artery, posterior cerebral artery, and anterior choroidal artery. The collaterals of these arteries are divided into four

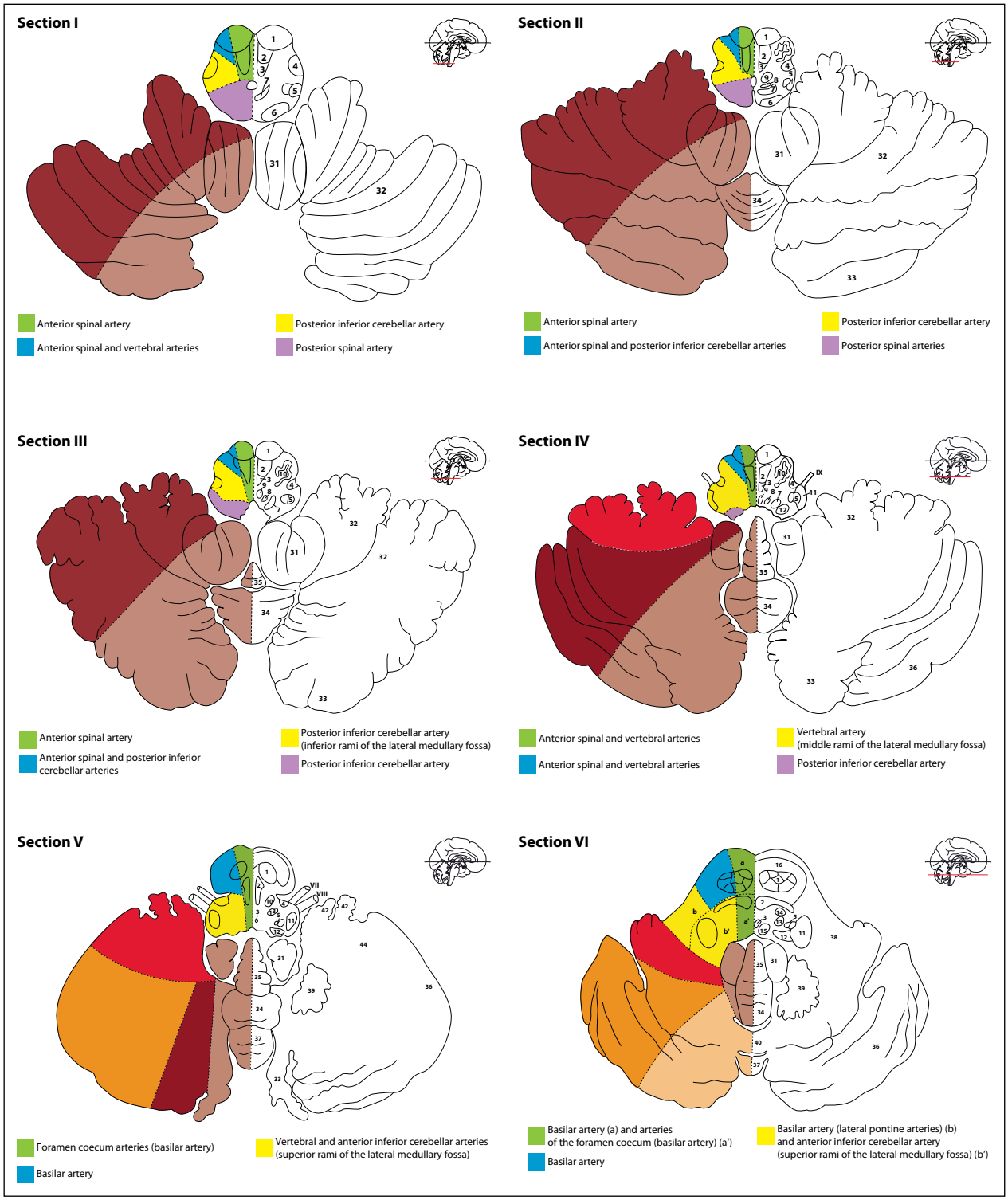


Fig. 1. Sections I–XII: arterial territories mapping: brainstem and cerebellum. For abbreviations and color codes see pp. 105–107.

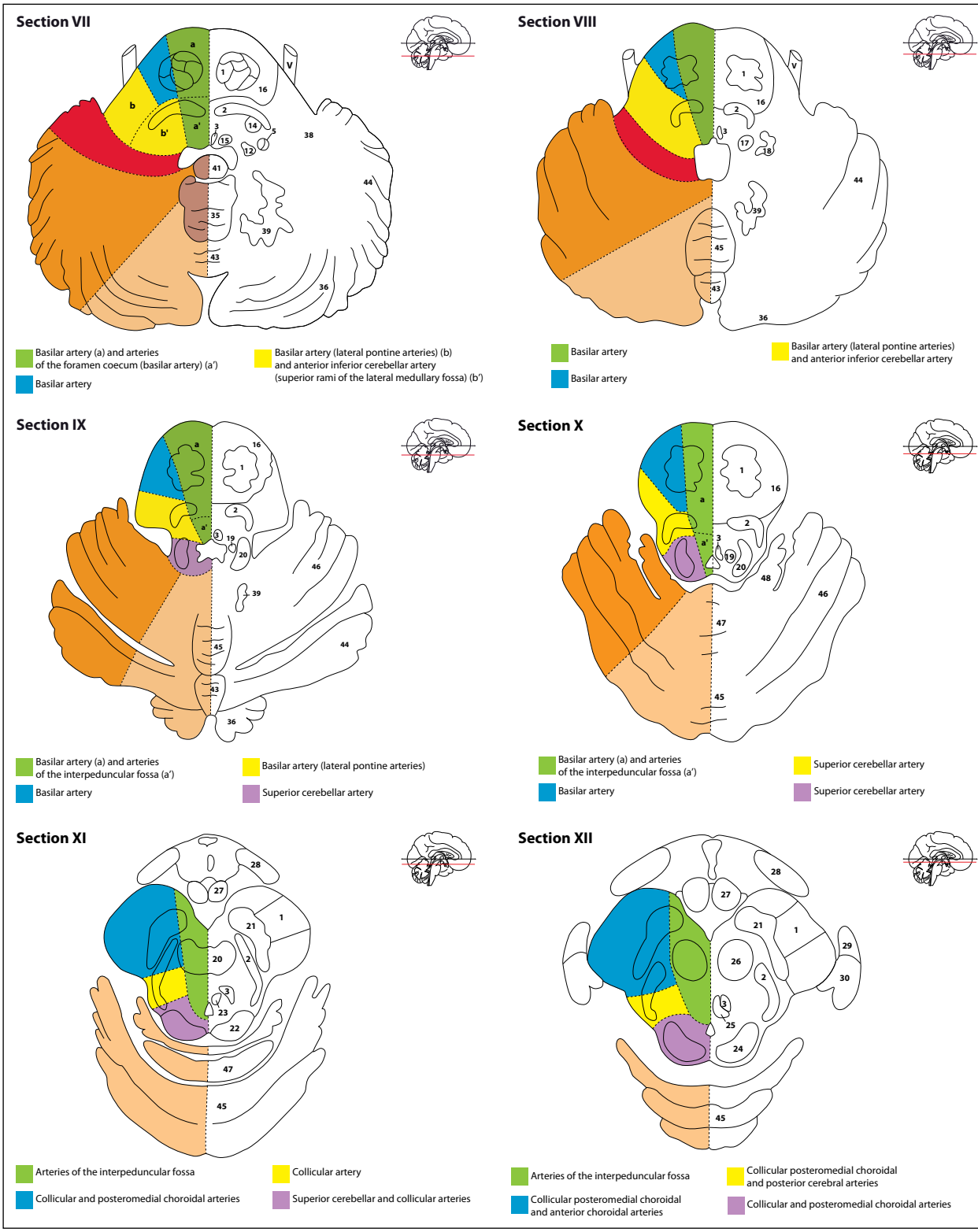


Fig. 1. Continued

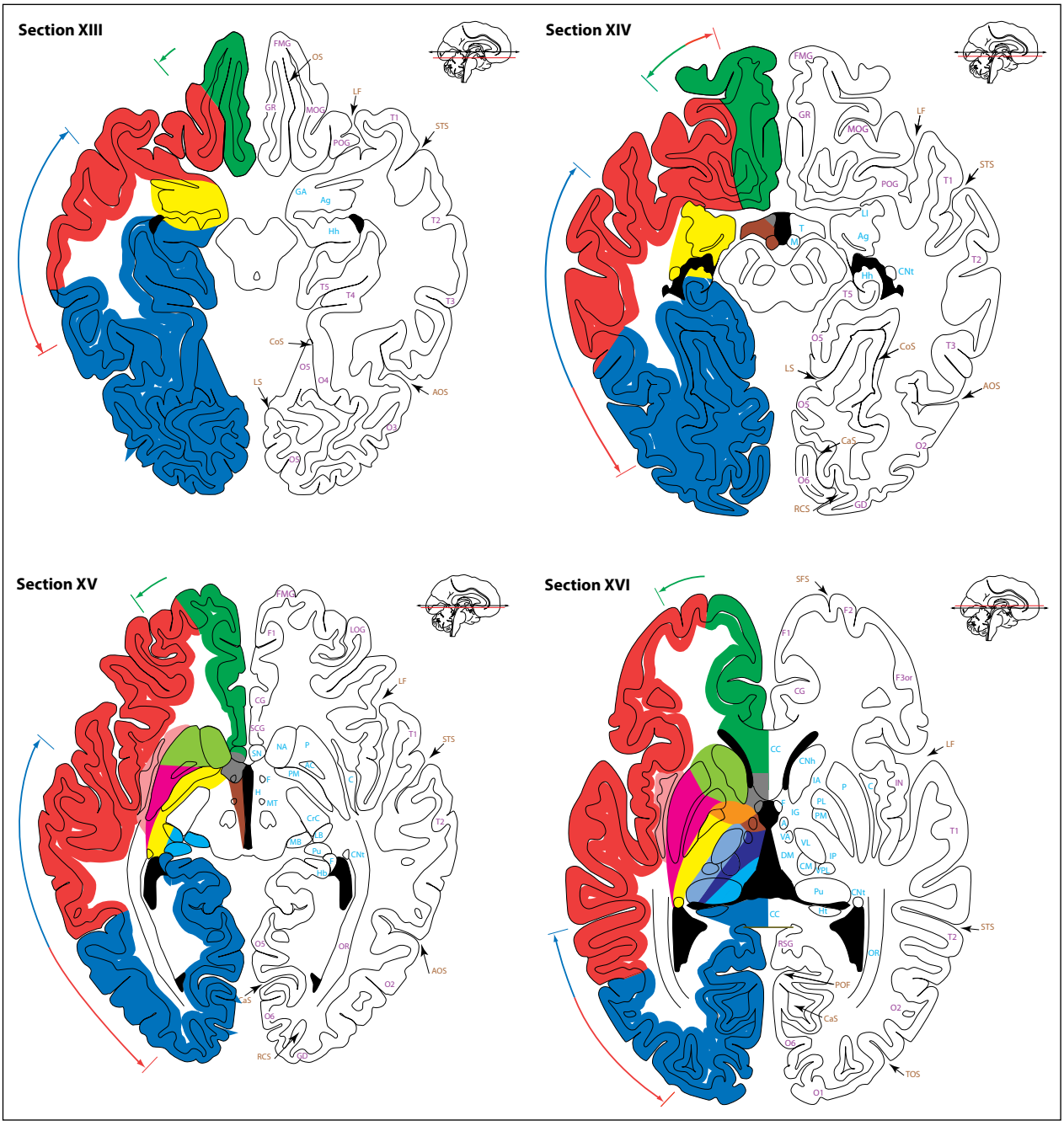
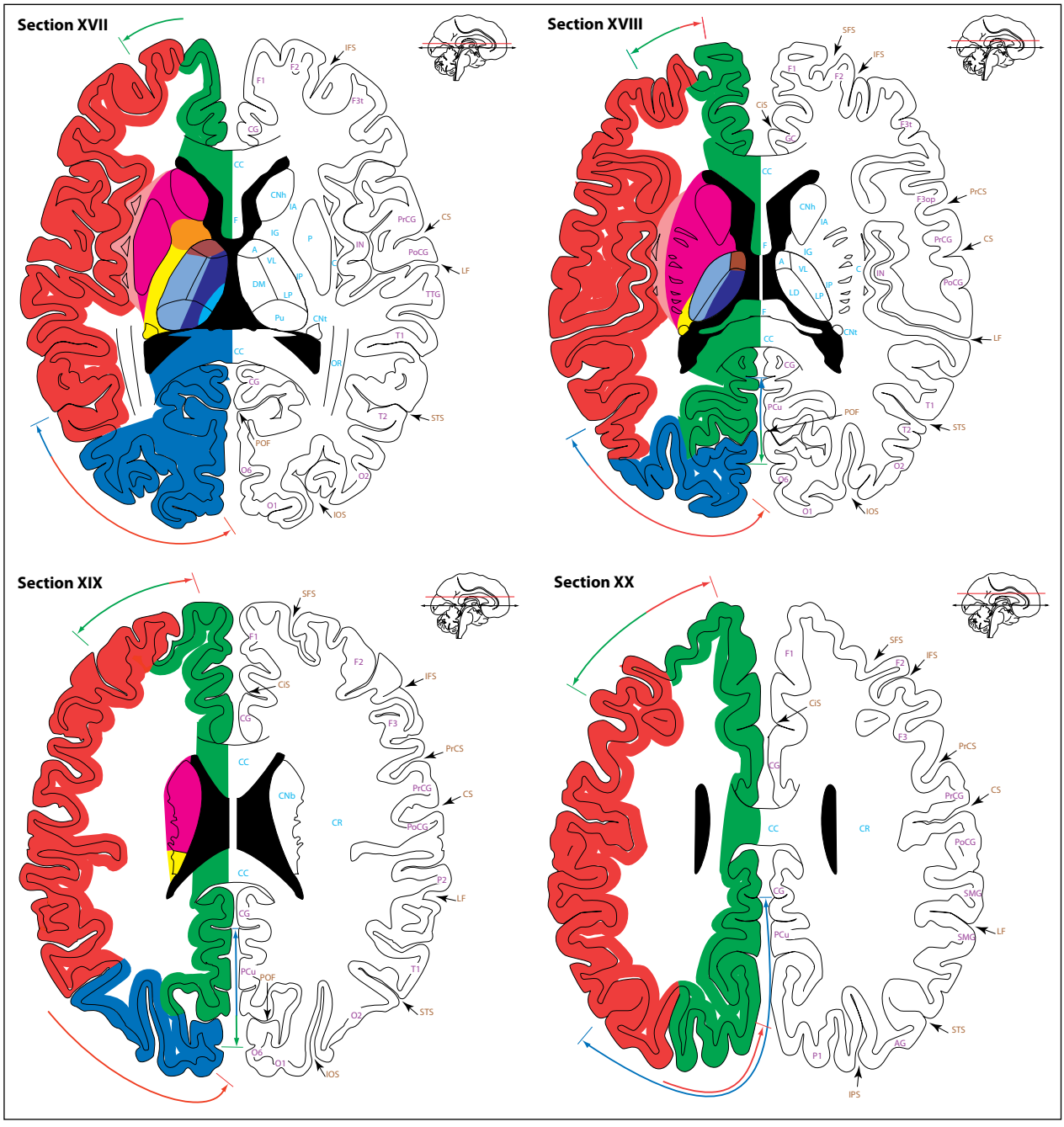


Fig. 2. Sections XIII–XXIV: arterial territories mapping: cerebral hemispheres. For abbreviations and color codes see pp. 105–107.



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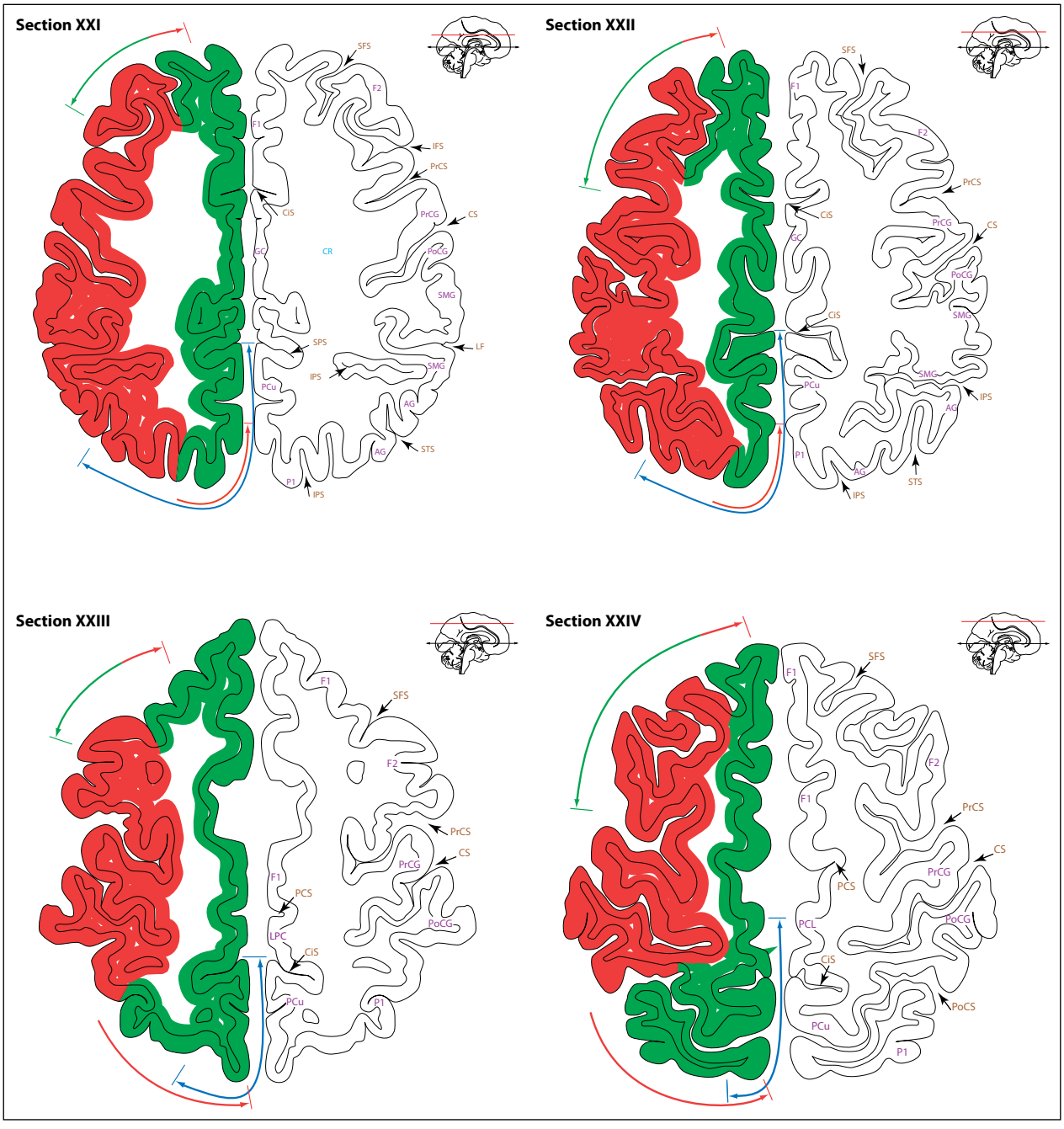


Fig. 2. Continued

Abbreviations: Anatomical structures of the brainstem and the cerebellum (sections I–XII)

1	Corticospinal tract
2	Medial lemniscus
3	Medial longitudinal fasciculus
4	Spinothalamic tract
5	Spinal trigeminal tract and nuclei
6	Gracile and cuneate nuclei
7	Nucleus of the solitary tract
8	Dorsal motor vagal nucleus
9	Hypoglossal nucleus
10	Inferior olivary nucleus
11	Inferior cerebellar peduncle
12	Vestibular nucleus
13	Facial nucleus
14	Superior olivary nucleus
15	Abducens nucleus
16	Pontine nuclei
17	Motor trigeminal nucleus
18	Principal sensory trigeminal nucleus
19	Nucleus coeruleus
20	Superior cerebellar peduncle
21	Sustantia nigra
22	Inferior colliculus
23	Trochlear nucleus
24	Superior colliculus
25	Oculomotor nucleus
26	Red nucleus
27	Mamillary body
28	Optic tract
29	Lateral geniculate body
30	Medial geniculate body
31	Tonsil
32	Biventer lobule
33	Inferior semilunar lobule
34	Pyramid of vermis
35	Uvula
36	Superior semilunar lobule
37	Tuber of vermis
38	Middle cerebellar peduncle
39	Dentate nucleus
40	Folium of vermis
41	Nodulus
42	Flocculus
43	Declive
44	Simple lobule
45	Culmen
46	Quadrangular lobule
47	Central lobule
48	Ala of the central lobule
V	Trigeminal nerve
VII	Facial nerve
VIII	Vestibulocochlear nerve
IX	Glossopharyngeal nerve

Abbreviations: Anatomical structures of cerebral hemispheres (sections XIII–XXIV)

Gyri (purple)

CG	Cingulate gyrus
F1	Superior frontal gyrus
F2	Middle frontal gyrus
F3	Inferior frontal gyrus
F3op	Inferior frontal gyrus pars opercularis
F3or	Inferior frontal gyrus pars orbitalis
F3t	Inferior frontal gyrus pars triangularis
FMG	Frontomarginal gyrus
GR	Gyrus rectus
LOG	Lateral orbital gyrus
MOG	Medial orbital gyrus
PCu	Precuneus
POG	Posterior orbital gyrus
SCG	Subcallosal gyrus
IN	Insula
PCL	Paracentral lobule
PoCG	Postcentral gyrus
PrCG	Precentral gyrus
AG	Angular gyrus
P1	Superior parietal gyrus
P2	Inferior parietal gyrus
SMG	Supramarginalis gyrus
T1	Superior temporal gyrus

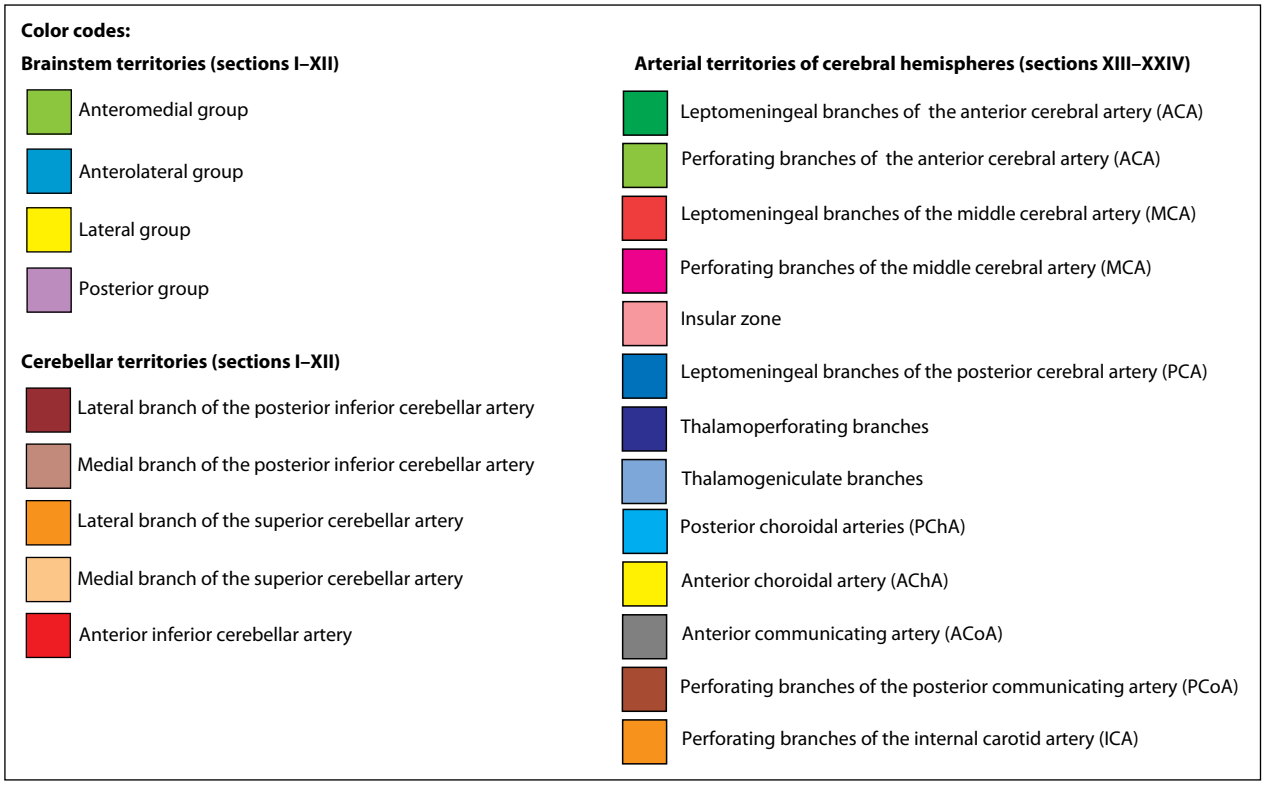
T2	Middle temporal gyrus
T3	Inferior temporal gyrus
T4	Fusiform gyrus
T5	Parahippocampal gyrus
TTG	Transverse temporal gyrus
O1	Superior occipital gyrus
O2	Middle occipital gyrus
O3	Inferior occipital gyrus
O4	Fusiform gyrus
O5	Lingual gyrus
O6	Cuneus
GD	Gyrus descendens (Ecker)
RSG	Retrosplenial gyrus

Sulci (brown)

AOS	Anterior occipital sulcus
CaS	Calcarine sulcus
CiS	Cingulate sulcus
CoS	Collateral sulcus
CS	Central sulcus
IFS	Inferior frontal sulcus
IOS	Intra-occipital sulcus
IPS	Intraparietal sulcus
LF	Lateral fissure
LS	Lingual sulcus
OS	Olfactory sulcus
PCS	Paracentral sulcus
PoCS	Postcentral sulcus
POF	Parieto-occipital fissure
PrCS	Precentral sulcus
RCS	Retrocalcarine sulcus
SFS	Superior frontal sulcus
SPS	Subparietal sulcus
STS	Superior temporal sulcus (parallel sulcus)
TOS	Transverse occipital sulcus

Internal structures (blue)

CNb	Caudate nucleus, body
CNh	Caudate nucleus, head
CNt	Caudate nucleus, tail
IA	Internal capsule, anterior limb
IG	Internal capsule, genu
IP	Internal capsule, posterior limb
NA	Nucleus accumbens
P	Putamen
PL	Globus pallidus, pars lateralis
PM	Globus pallidus, pars medialis
SN	Septal nuclei
A	Anterior thalamic nucleus
CM	Centromedian thalamic nucleus
DM	Dorsomedial thalamic nucleus
LD	Lateral dorsal thalamic nucleus
LP	Lateral posterior thalamic nucleus
Pu	Pulvinar
VA	Ventral anterior thalamic nucleus
VL	Ventral lateral thalamic nucleus
VPL	Ventral posterolateral thalamic nucleus
C	Claustrum
CR	Corona radiata
IN	Insula
LI	Limen insulae
CC	Corpus callosum
F	Fornix
Hb	Hippocampus, body
Hh	Hippocampus, head
Ht	Hippocampus, tail
AC	Anterior commissure
Ag	Amygdala
CrC	Crus cerebri
GA	Gyrus ambiens
H	Hypothalamus
LB	Lateral geniculate body
M	Mamillary body
MB	Medial geniculate body
MT	Mamillo-thalamic tract
OR	Optic radiations
T	Tuber



arterial groups (anteromedial, anterolateral, lateral and posterior) according to their point of penetration into the parenchyma. Each of these groups supplies the corresponding arterial territories in the brainstem. The arterial territories have a variable extension at different levels of the brainstem.

Arterial Groups Supplying the Medulla

The medulla is supplied by the vertebral arteries and the posterior inferior cerebellar artery, which give rise to the rami of the lateral medullary fossa, and by the anterior and posterior spinal arteries.

Arterial Groups Supplying the Pons

Different arterial trunks supply blood to the pons including the vertebral artery, the anterior inferior cerebellar artery, from which arise the rami of the lateral medullary fossa, the superior cerebellar artery and the basilar artery. The anteromedial pontine territory is supplied by distinct arterial sources arising from different levels of the basilar artery. These sources include foramen caecum arteries, pontine arteries and inferior rami arising from the interpeduncular fossa arteries. This point is crucial to understanding the clinical signs of alternate pontine infarction syndromes. The posterior territory only exists in the upper part of the pons.

Arterial Groups Supplying the Midbrain

Five arterial trunks supply the midbrain: the superior cerebellar artery (mainly the medial branch), the collicular artery, the posteromedial choroidal artery, the middle rami of the interpeduncular arteries arising from the posterior cerebral artery

and the anterior choroidal artery arising from the carotid system.

Arterial Supply of the Cerebellum

The cerebellum is supplied by the three long cerebellar arteries: posterior inferior cerebellar artery, anterior inferior cerebellar artery and superior cerebellar artery.

The posterior inferior cerebellar artery originates from the vertebral artery. It gives off medial and lateral branches and supplies the inferior vermis as well as the inferior and posterior surfaces of the cerebellar hemispheres. The posterior inferior cerebellar artery also forms part of the lateral and posterior groups of the medulla, either via its common stem or its medial branch.

The anterior inferior cerebellar artery usually arises from the bottom third of the basilar artery and supplies the anterior surface of the simple, superior and inferior semilunar lobules as well as the flocculus. In most cases, it gives rise to the internal auditory artery. The anterior inferior cerebellar artery contributes to the supply of the middle cerebellar peduncle and often the lower part of the pontine tegmentum.

The superior cerebellar artery – also known as the anterior superior cerebellar artery – divides into medial and lateral branches and supplies the superior half of the cerebellar hemisphere and vermis as well as the dentate nucleus. The superior cerebellar artery territory often includes the upper part of the pontine tegmentum.

Arterial Supply of Cerebral Hemispheres

The cerebral arteries are divided into perforating and cortical arteries. The perforating arteries (or deep perforating arteries) arise from the arterial circle of Willis or from its immediate branches and directly penetrate the brain parenchyma. The internal carotid artery, anterior choroidal artery, anterior communicating artery, anterior cerebral artery, middle cerebral artery, posterior communicating artery and posterior cerebral artery all give rise to perforating arteries.

The cortical arteries (also known as leptomeningeal, superficial or pial) consist of the terminal branches of the anterior, middle and posterior cerebral arteries, which form an anastomotic network on the surface of the hemispheres. Their branches penetrate the cortex, subjacent white matter and U-fibers. The deepest of these branches form the medullary (or superficial perforating) arteries and participate in centrum ovale vascularization.

Several points relating to the arterial circulation of the cerebral hemispheres still need to be elucidated including the vascular organization of the centrum ovale or the peri-insular region.

Perforating Branches of the Cerebral Arteries

Perforating Branches of the Internal Carotid Artery

Some perforating arteries arise from the supraclinoid portion of the internal carotid artery, pass through the anterior perforated substance to supply the genu of the internal capsule, the adjacent part of the globus pallidus and the contiguous posterior limb of the internal capsule.

Perforating Branches of the Anterior Choroidal Artery

The perforating territory of this artery, arising from the supraclinoid portion of the internal carotid artery, includes the lower part of the two posterior thirds and the retrolenticular part of the internal capsule, the adjacent optic radiations and acoustic radiations, the medial globus pallidus and the tail of the caudate nucleus.

Perforating Branches of the Anterior Communicating Artery

The vascular territory of this artery includes the lamina terminalis, the anterior hypothalamus,

the septum pellucidum, part of the anterior commissure and of the fornix, the paraterminal gyrus including the septal nuclei and occasionally the subcallosal region, the anterior part of the corpus callosum and the cingulate gyrus.

Perforating Branches of the Anterior Cerebral Artery

The direct perforators of the anterior cerebral artery usually arise from the proximal pre-communicating segment, and the recurrent artery of Heubner from the proximal post-communicating segment. These arteries supply the anterior and inferior part of the head of the caudate nucleus, the anterior and inferior portions of the anterior limb of the internal capsule, the adjacent part of the putamen and globus pallidus, the caudal rectus gyrus, the subcallosal gyrus and the medial part of the anterior commissure.

Perforating Arteries of the Middle Cerebral Artery

These are the lenticulostriate arteries arising from the basal segment of the middle cerebral artery. They are usually classified into two groups: the medial and the lateral arteries. These perforating branches supply the superior part of the head and the body of the caudate nucleus, the lateral segment of the globus pallidus, the putamen, the dorsal half of the internal capsule and the lateral half of the anterior commissure.

Perforating Branches of the Posterior Communicating Artery

Some branches arise from the posterior communicating artery. The largest branch is termed the premamillary artery (anterior thalamoperforating artery or tuberothalamic artery). These branches supply the posterior portion of the optic chiasm and optic tract, the posterior part of the hypothalamus, the mamillary body, the nucleus anterior and the polar part of the nucleus ventralis anterior of the thalamus.

Thalamoperforating Branches

The thalamoperforating arteries (or paramedian thalamic arteries) form the superior rami of the interpeduncular arteries and contribute to the supply of the thalamus. They supply the medial nuclei, the intralaminar nuclei, part of the dorsomedial nucleus, the posteromedial portion of the lateral nuclei and the ventromedial pulvinar.

Thalamogeniculate Branches

The thalamogeniculate arteries (or inferolateral thalamic arteries) usually arise from the posterior cerebral artery segment in proximity to the geniculate bodies and take part in the surrounding arterial anastomotic network. They supply a major part of the lateral side of the caudal thalamus including the rostrolateral part of the pulvinar, the posterior part of the lateral nuclei and lateral dorsal nucleus, and the ventral posterior and ventral lateral nuclei.

Perforating Branches of the Posterior Choroidal Arteries

The posterior choroidal group usually arises from perimesencephalic segments of the posterior cerebral artery and includes one medial and several lateral posterior choroidal arteries. The medial posterior choroidal artery supplies the medial geniculate body, as well as the posterior part of the medial nucleus and of the pulvinar. The lateral posterior choroidal artery supplies part of the lateral geniculate body, part of the thalamic dorsomedial nucleus and part of the pulvinar.

Cortical Branches of the Cerebral Arteries

Cortical Branches of the Anterior Cerebral Artery

These branches arise from the distal segment of the anterior cerebral artery, also called the pericallosal artery, which gives rise to cortical and callosal branches. The callosal branches supply

the rostrum, genu and body of the corpus callosum. In most cases, the cortical branches supply the cortical area of the medial surface of the hemisphere extending to the superior frontal sulcus and the parieto-occipital sulcus. On the orbitofrontal surface, the arterial territory includes the medial orbital gyri. At most the cortical anterior cerebral artery territory reaches the inferior frontal sulcus and at least, it includes only the anterior part of the frontal lobe.

Cortical Branches of the Middle Cerebral Artery

These cortical branches most commonly distribute to the area on the lateral surface of the hemisphere that extends to the superior frontal sulcus, the intraparietal sulcus and the inferior temporal gyrus. On the orbitofrontal surface, the arterial territory includes the lateral orbital gyri. The maximum area covers the whole lateral surface of the hemisphere, reaching the interhemispheric fissure and the minimum area is confined to the territory between the inferior frontal and the superior temporal sulci.

Cortical Branches of the Posterior Cerebral Artery

These branches include the hippocampal arteries and the splenial artery which anastomose with the distal part of the pericallosal artery to supply the splenium of the corpus callosum. The most common cortical distribution of these arteries includes the inferomedial surfaces of the temporal and the occipital lobes extending to the parieto-occipital fissure. The maximum area can extend as far as the superior temporal sulcus and the upper part of the precentral sulcus, and the minimum area extends only as far as the medial face of the occipital lobe limited by the parieto-occipital fissure.

Cortical Branches of the Anterior Choroidal Artery

The cortical territory of the anterior choroidal artery includes part of the uncus, part of the head of the hippocampus, part of the amygdaloid nucleus and the lateral part of the lateral geniculate body.

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Superficial Middle Cerebral Artery Territory Infarction

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Abstract

The superficial middle cerebral artery (MCA) territory includes the greater part of the lateral surface of the cerebral hemisphere. It is the most frequent infarct in MCA ischemic cerebrovascular pathology. It is divided into 12 areas supplied by 12 different arteries referred to as the irrigated areas; however, anatomical variations should be considered in these infarcts. Clinical symptomatology depends on the artery affected (changes in personality, judgment or motor synchronization disturbances, disorientation, hemianopia or hemineglect), but more frequently there is an overlapping of artery infarcts (insular syndrome and sensitive, motor or language disturbances). Embolic mechanism remains the main etiology of these infarcts, but due to different etiological mechanisms of ischemic stroke, an extensive neurovascular and cardiological assessment is essential for the correct treatment of the patient.

The most frequently affected territory in ischemic cerebrovascular pathology is the middle cerebral artery (MCA) territory [1], which may be divided into superficial and profound territory according to anatomical considerations.

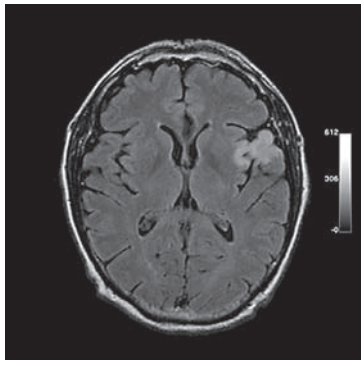
Superficial Middle Cerebral Artery

The superficial MCA territory includes the greater part of the lateral surface of the hemisphere that extends to the inferior surfaces of the frontal and temporal lobes [2, 3]. It is divided into 12 areas supplied by 12 different arteries referred to as the irrigated areas: orbitofrontal, prefrontal, precentral, central, parietal (anterior and posterior), temporopolar, angular, temporal (anterior, middle and posterior) and temporo-occipital [3]. These arteries normally emerge from 2 trunks (less frequently from 3): superior or anterior (orbitofrontal, prefrontal, precentral and central arteries), and the inferior or posterior trunk (temporopolar, temporo-occipital, angular, and anterior, middle and posterior temporal arteries) [3]. The anterior and posterior parietal arteries usually arise from the dominant trunk. All of these anatomical variations should be considered in ischemic pathology.

Etiology of the Superficial Middle Cerebral Artery Infarct

Several MCA infarct production mechanisms have been described. Embolism is a common etiology in MCA infarcts, and severe MCA stenosis or occlusion is associated with any superficial infarct pattern, resulting in a higher risk of artery-to-artery embolization than milder MCA stenosis [4].

Neuroimaging helps in etiological diagnosis in patients with MCA infarcts (fig. 1–4). The most common brain CT or MRI location of MCA



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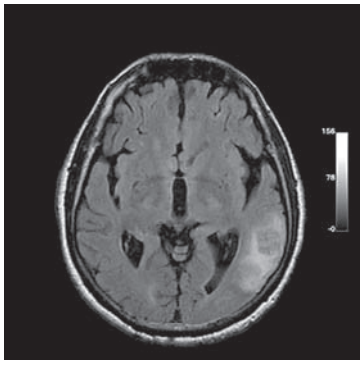

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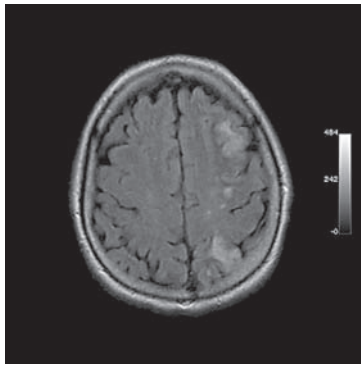

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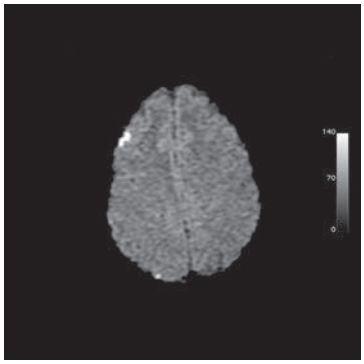

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Fig. 1. Cranial MR FLAIR T_2 sequences show a left insular ischemic lesion (anterior or superior trunk) in a 59-year-old male with interatrial communication admitted due to motor dysphasia.
Fig. 2. Cranial MR FLAIR T_2 sequences show a left temporoparietal ischemic lesion (posterior or inferior trunk) in a 67-year-old male with sensitive dysphasia and atrial fibrillation.
Fig. 3. Cranial MR FLAIR T_2 sequences show a left parietal ischemic lesion in a 43-year-old female with an intracranial internal carotid dissection admitted due to headache and behavioral impairment.
Fig. 4. Cranial MR diffusion sequences show small right cortical parietal ischemic lesions in a 40-year-old male without any cerebrovascular risk factor admitted due to left hemiparesis.

territory infarct is cortical in more than 50% of cases [5], and may be even higher due to the specific MRI sequences that permit the diagnosis of small cortical infarcts. The localization and the size of infarction by neuroimaging are different in patients with intrinsic disease than in patients with embolism and carotid disease [5]. In patients with intrinsic MCA disease, the mechanism of cortical infarcts is impaired distal perfusion or distal embolism [5], so small multiple cortical infarcts in the same arterial territory are attributed to fragmentation of an embolus located within a major proximal intracranial artery [6]. However, multiple infarcts located in one or more major arterial territories of the anterior and/or posterior circulation are produced from embolic sources proximal to the cervical arteries [6]. In the New England Medical Center Stroke Registry, cortical infarcts were seen in 26.2% of carotid artery disease, 17.4% cases of MCA intrinsic disease and 6.3% of MCA embolic disease. The superior or anterior trunk was affected more frequently (62.5%) than the inferior or posterior trunk (50%) in embolic mechanism [6]. In the Lausanne Stroke Registry, the presumed cause of cortical infarcts was large-artery disease (>50% carotid artery or MCA stenosis or occlusion) in 34% of the patients, without differences between anterior and posterior infarcts. Cardioembolism was observed in 24.5% of the patients, more frequently in those with inferior or posterior infarct than superior or anterior infarct [7].

Clinical Manifestations of the Superficial Middle Cerebral Artery Infarct

As has been previously described, the extension of superficial territory infarcts depends on the status of collateral supply and on the arterial distribution

pattern of superior or anterior and inferior or posterior trunks of the MCA [8]. In a few cases the inferior or posterior trunk supplied the temporal and parietal lobes and extended to the precentral motor area. In other cases a large superior or anterior trunk supplied the frontal and parietal lobes and extended to the speech centers on the posterior part of the temporal lobe [3]. Disability is more common in patients with posterior infarcts than in patients with anterior ones, mainly arising from persisting neuropsychological dysfunction or proprioceptive loss in the upper limb [7].

The MCA territory infarct may mimic lacunar infarct in 2% of cases [7] and it is very difficult to establish a single clinical pattern for every single cortical artery. Nevertheless, some symptoms point towards a specific artery infarct: changes in personality due to involvement of prefrontal artery; disturbances of judgment, insight and mood due to involvement of orbitofrontal and prefrontal arteries or disturbances in motor coordination due to involvement of precentral artery [9]. More commonly there is an overlapping of artery infarcts causing certain syndromes in which left hemisphere lesions are associated with aphasia and apraxia, while right hemisphere lesions are associated with hemineglect, anosognosia, visual agnosia and visuospatial deficits [1]:

Opercular Syndrome (Foix-Chavany-Marie Syndrome). The arterial supply of the insula is exclusively from cortical branches of the MCA, the anterior insula from branches of the superior MCA trunk and the posterior insula from branches of the inferior MCA trunk. Dysarthria, dysphagia and dysphonia are observed because signals to the V, VII and IX cranial nerves are affected in the insular cortex. This is described as pseudobulbar palsy with bilateral insular lesions and is differentiated from pontine or capsulostriatal pseudobulbar palsy by the absence of mental impairment and sphincter incontinence [9]. The most frequent cause of insular infarct is cardioembolism [5].

Aphasia. The left central artery infarct produces Broca's aphasia and less commonly, left precentral artery infarct produces transcortical motor aphasia. No specific cause has been described for these types of infarct. Left temporal or temporo-occipital artery infarct produces Wernicke's aphasia and is suggestive of embolism (artery-to-artery and cardioembolism) [7]. Dysarthria and Broca's aphasia are more common in anterior infarcts and Wernicke's aphasia in posterior infarct. Global aphasia may be seen in anterior and posterior infarcts, but it rapidly evolves towards a Broca's or Wernicke's aphasia, depending on the territory affected [7].

Motor Syndrome. Contralateral weakness of face, arm, trunk and hip is caused by central area involvement. The leg can be weakened but usually less severely and more transiently than is seen in ACA infarct [9]. Faciobrachial involvement is the most common manifestation, both in patients with anterior and with posterior infarcts [7]. No specific cause has been described for these types of infarct.

Sensory Syndrome. Contralateral sensitive impairment in the face, arm, trunk and hip, and occasionally of the leg is seen as a consequence of the involvement of the parietal area. This has been called cortical sensory loss (disturbances in the sense of position, touch, localization, stereognosis, ascertainment of shape, size and texture, two-point discrimination and graphesthesia) and has to be differentiated from the loss of primary sensory perception (pain, temperature, vibration and touch) found in lesions in the lateral striate territory [9]. No specific cause has been described for these infarcts.

Angular Gyrus Syndrome. Left superior angular and supramarginal gyrus lesions produce *Gerstmann's syndrome* with acalculia, agraphia, right-left disorientation and finger agnosia. In right hemispheric lesions, spatial neglect, extinction on bilateral simultaneous stimulation, asomatognosia, visuospatial disturbances and constructional apraxia are frequent. In bilateral lesions *Balint's syndrome* may be found with gaze paralysis, visual inattention and optic ataxia [1].

Conclusions

The superficial MCA is the most frequent infarct in MCA ischemic cerebrovascular pathology. Anatomical variations should be considered in these infarcts. Some clinical symptomatology and syndromes may point towards a specific cause, but due to different etiological mechanisms of ischemic stroke, an extensive neurovascular and cardiological assessment is essential for the correct treatment of the patient.

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Lenticulostriate Infarction

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Abstract

Lenticulostriate infarcts result from ischemia within the territory supplied by the deep perforating branches of the middle cerebral artery (MCA). They are too often associated with infarctions of the deep perforating branches of the internal carotid artery. Lenticulostriate arteries usually arise from the main trunk of the MCA, but can emerge from the cortical branches. The clinical aspects of lenticulostriate infarction should be properly differentiated from those of other anterior circulation infarcts. Clinical signs include motor deficit, sensory deficit and cognitive dysfunction. The principal mechanism for lenticulostriate infarction seems to be an embolism of cardiac origin. The concept of lacunar infarctions relating to lipohyalinosis is perhaps too often proposed without evidence. The prognosis is dependent primarily on the intensity of damage to the upper part of the posterior limb of the internal capsule. They are terminal arteries without anastomoses, making them more susceptible to ischemia and resulting in a greater risk of arteriolar necrosis and hemorrhagic transformation.

Lenticulostriate infarctions are defined as cerebral ischemia involving the territory supplied by the deep perforating branches of the middle cerebral artery (MCA), also known as the lenticulostriate arteries. They represent approximately 11–13% of cerebral infarctions related to anterior circulation [1–3]. Although the territory supplied by the lenticulostriate arteries is well defined, it is often associated with the territory of the anterior choroidal artery and is usually included within the category of deep perforating arteries of the carotid artery [4]. This explains why the clinical features, prognosis and management are not particularly well known or clearly defined. Lastly, the specific physiopathological implications, relating to supply by terminal arteries without anastomoses, are still unclear.

Anatomical and Physiopathological Background

The lenticulostriate territory supplies the upper part of the head and the body of the caudate nucleus, the putamen, the lateral part of the pallidum, the superior part of the anterior and posterior limbs and the genu of the internal capsule, and the lateral third of the anterior commissure. This territory is in balance with the territories of the other perforating arteries of the internal carotid, anterior cerebral and anterior choroidal arteries [5, 6].

The MCA, which is the principal branch resulting from the division of the internal carotid artery, enters the lateral fissure after a 90° change of direction and usually divides into two trunks (superior and inferior) giving rise to the cortical branches. The perforating branches of the MCA,

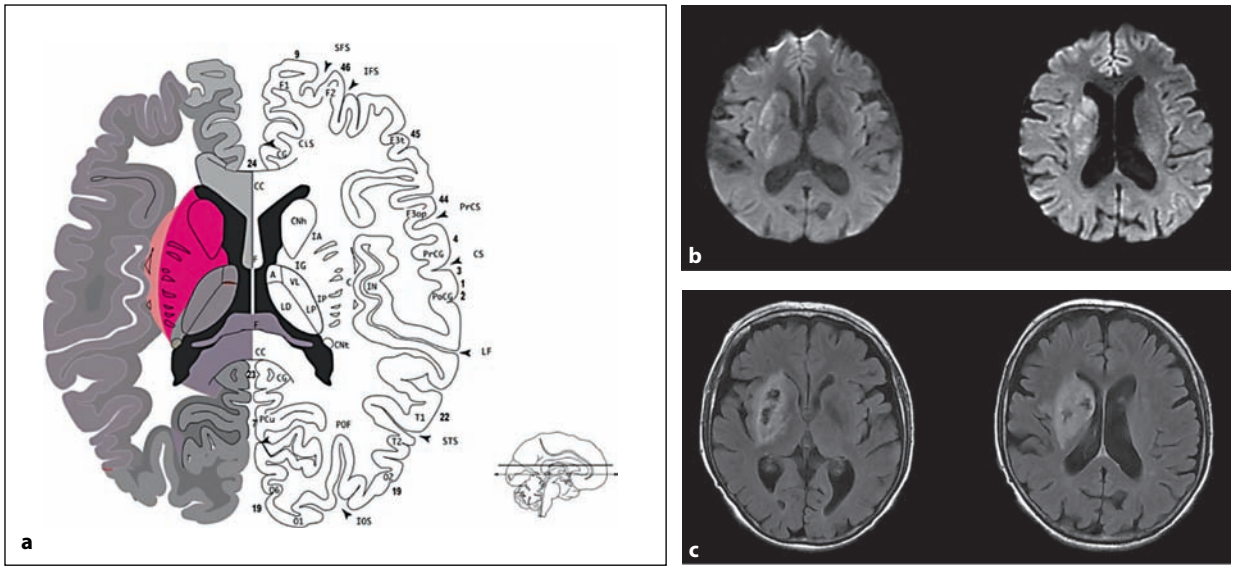

Fig. 1. **a** Arterial mapping of the lenticulostriate territory (from Tatu et al. [4]). **b** Lenticulostriate infarct in DWI sequence. **c** Lenticulostriate infarct in FLAIR sequence.

known as lenticulostriate arteries, usually arise from the main trunk of the MCA before the bifurcation [7, 8]. However, the origin of these perforating branches can vary and in a considerable number of cases they emerge from the cortical branches. They can also emerge from the early cortical branches of the MCA, in which case they are defined as cortical arteries arising from the M1 segment [8, 9]. Many classifications for the perforating branches of the MCA have been proposed, generally based on the division of the lenticulostriate arteries into two or three groups [6, 7]. Nevertheless, they are usually classified into two groups – the medial and lateral arteries [10]. However, this disposition is variable and a common stem may be present.

Clinical Aspects

Motor deficit is severe and present in all cases. It almost always affects the entire hemibody (in 86% of cases) [3, 11] and the proximal part of the limbs is also affected [12, 13]. In some cases, the effect on motricity is partial and limited to motor disability. The severity of motor deficit depends on the extent of the infarct in the upper part of the internal capsule. This has been confirmed through work with MRI fiber tracking [14].

From the onset and within the first few hours, the clinical evolution of motricity is often characterized, in approximately half of cases, by a rapid worsening of the motor deficit. The posterior extent and size of the infarct are important factors in predicting this adverse development [15–18]. Sensory deficit is less common and is noted in 30% of lenticulostriate infarcts. It is dependent on the lateral and posterior extent of the infarct [3]. Cognitive dysfunction occurs relatively often, in 30–80% of cases [1, 3, 19, 20]. Such neuropsychological features correspond to motor aphasia in left-side infarcts, an anosognosia and neglect in right-side infarcts or, less frequently, frontal syndromes [21]. A pure mutism has been reported in

the context of a bilateral lenticulostriate infarcts [22]. The curious 'gourmand syndrome' is less common and is described as pathological alimentary behavior and an abnormal interest in food [23].

Several hypotheses have been proposed to explain the presence of neuropsychological dysfunction associated with lenticulostriate infarction [24], namely a cortical disconnection, a diaschisis, a cortical hypoperfusion or even an incomplete cortical involvement. The most valid hypothesis seems to be related to a cortical hypoperfusion [11, 20, 24, 25]. However, cortical involvement is not uncommonly associated with lenticulostriate infarctions [26]. These cortical infarctions can be explained by the cortical origin of the lenticulostriate arteries described in 20% of cases [6, 9].

Etiologies

The principal mechanism for lenticulostriate infarction seems to be an embolism of cardiac origin. A cardiac abnormality is found in nearly 50% of cases [25]. Proximal occlusion of the internal carotid artery is found in 18–35% of cases, inducing a hemodynamic change or a distal embolism [27]. A proximal stenosis of the M1 segment of the MCA can lead to the occlusion of the ostium of its perforating branches or an artery-to-artery embolism [28]. The role of localized atheroma on the ostium of the perforating arteries is probably underestimated [29], just as the 'lacunar' origin, i.e. specifically related to arteriolar degeneration by lipohyalinosis, is overestimated [20].

The risk factors for major lenticulostriate infarction are identical to those in other arterial territories and differ from the risk factors for lacunar infarction (hypertension or diabetes) [19]. Arterial anomalies in the MCA (stenosis, occlusion) seem to lead to larger proximal infarctions of a greater volume. In the absence of any anomalies in the M1 segment of the MCA, lesions are considerably more distal and of a low volume, indicating a lacunar origin [30].

Prognosis

In general, the prognosis for cerebral ischemia should be evaluated from the acute phase using clinical, biological and neuroimaging criteria. Thus, statistical models have enabled the relevant elements and their relative risks to be defined, and have highlighted the importance of both a clinical score (NIHSS) and lesion volume defined by diffusion-perfusion MRI [31]. Specifically, very few cohorts have studied the morbi-mortality of lenticulostriate infarcts [2]. Overall, mortality is less than 10%. It is similar to that found in partial cortical infarcts, and much lower than that in total MCA infarcts [12].

Motor recovery is particularly dependent on the damage to the upper part of the posterior limb of the internal capsule [14, 32]. In the series that specifically analyzed infarction involving the posterior limb of the internal capsule, including both the lenticulostriate territory and the anterior choroidal territory, motor recovery remains limited [31–34]. The quality of motor recovery is inversely proportional to the size of the ischemic lesion [34]. In particular, it is linked to the intensity of the damage to the corticospinal tract as shown in MRI tractography [33].

The initial course and motor recovery are also affected by the particularly frequent occurrence of a hemorrhagic transformation (HT), either spontaneously or in relation to an antithrombotic medication. HT is related in particular to vascular reperfusion or even to an intrainfarct hematoma resulting from a vascular rupture [35]. The lenticulostriate territory is particularly susceptible to HT following thrombolysis [36]. The terminal nature of these deep perforating branches could explain their greater susceptibility to ischemia, as recently demonstrated by the hyperpermeability index identified in perfusion images [37].

Conclusion

In the territory supplied by the lenticulostriate arteries, small volume infarctions should be considered as small volume territorial infarctions resulting from abnormalities in the terminal arteries. The concept of lacunar infarctions relating to lipohyalinosis is perhaps too often proposed without evidence. The physiopathology should be more accurately identified, given the therapeutic implications. Finally, technical developments in neuroimaging would allow the various lenticulostriate territories to be better defined according to the distribution of the different deep perforating branches.

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Anterior Cerebral Artery and Heubner's Artery Territory Infarction

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Abstract

Anterior cerebral artery (ACA) territory strokes account for 0.5–3% of all ischemic strokes. The etiological mechanisms of ACA territory strokes vary by race; ACA dissection is a frequent cause in Japan. The most prevalent symptom of such strokes is contralateral hemiparesis or monoparesis, usually affecting the leg predominantly. Predominant leg weakness is attributed to damage in the paracentral lobule, and weakness of the arm and face is associated with involvement of Heubner's artery and the medial striate arteries. Hypobulia, typically 'akinetic mutism', is also common. Several behavioral disorders, including the grasp reflex and the alien hand sign, can present as callosal disconnection signs. Transcortical aphasia and urinary incontinence are other frequent symptoms. A non-throbbing headache is common at stroke onset in patients with ACA dissection.

Cerebral infarcts localized in the anterior cerebral artery (ACA) territory are relatively rare, accounting for 0.5–3% of all ischemic strokes [1–7]. Some investigators reported that embolism from the heart or carotid arteries is the leading mechanism [1, 2, 4], while others from Eastern Asia reported a high prevalence of intrinsic ACA atherosclerosis [3, 5]. Our recent study on consecutive Japanese patients with isolated ACA territory infarction showed that 18 of 42 patients (43%) had ACA dissection verified on digital subtraction angiography [6] (fig. 1). A nationwide survey in Japan showed that, among patients with cervicocephalic arterial dissection, there was a relatively high percentage of intracranial dissection, including that involving the ACA [7].

The ACA is divided into the proximal segment (A1), the ascending segment (A2, A3), and the horizontal segment (A4, A5). The anterior communicating artery (ACoA) arises at the end of A1 and connects the bilateral ACAs. Sometimes, the A1 segment is absent or hypoplastic, and the contralateral ICA supplies the ACA territory via the ACoA. The recurrent artery of Heubner and other medial striate arteries arise near the origin of the ACoA and supply the anteromedial portion of the caudate nucleus, the anterior limb of the internal capsule, and the anterior perforated substance. The distal ACA divides into the pericallosal and callosomarginal arteries and supplies the paramedian frontal lobe, including the corpus callosum, cingulate gyrus, frontal pole/gyrus rectus, medial aspect of the superior frontal gyrus, supplementary motor area, paracentral lobule, and precuneus [5].

According to magnetic resonance imaging studies, infarcts occur predominantly on the left side [4–6]. In these studies, bilateral ACA infarcts were identified in 0–9% of all patients with

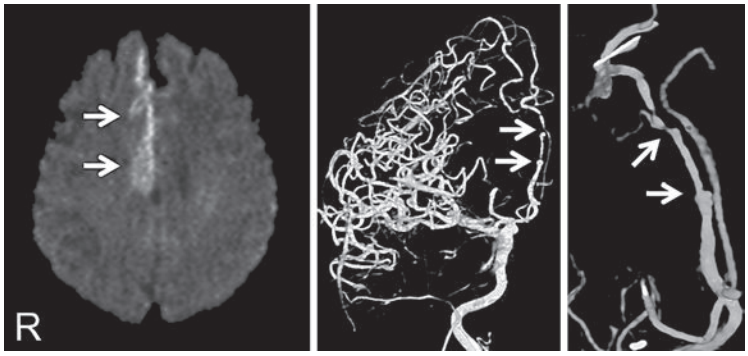

Fig. 1. Representative image of a fresh infarct in the right ACA territory (left panel, diffusion-weighted image) and three-dimensional rotational angiograms showing the right ACA dissection with the 'pearl-and-string' sign (aneurysmal dilatations followed by segmental stenosis) of the A2 segment (middle and right panels). Images of the patient described in Sato et al. [6].

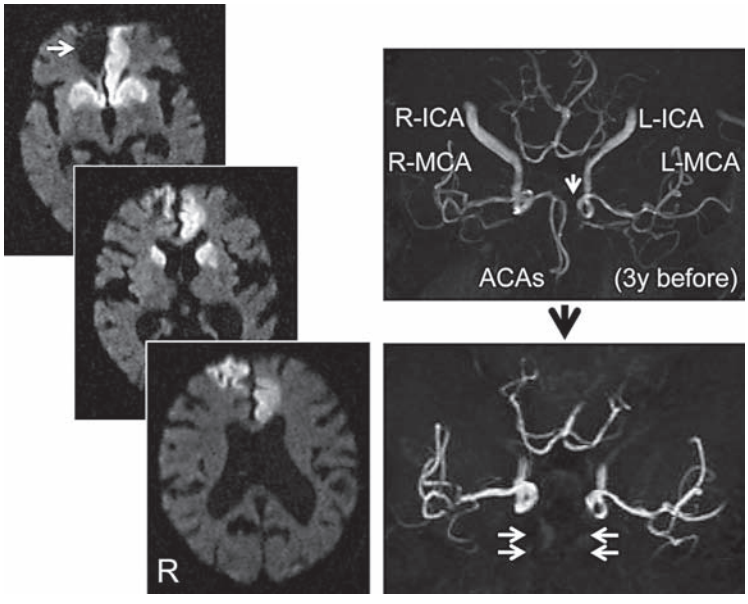

Fig. 2. Representative images of fresh cardioembolic infarcts in the bilateral ACA territories (left panel, diffusion-weighted images) with an old infarct in the terminal branches of the right ACA territory (arrow). This patient with atrial fibrillation was diagnosed as having intact ACAs except for absence of the left A1 segment (arrow) on magnetic resonance angiography (MRA) 3 years before (right top panel). This time, MRA does not reveal either side of ACA (arrows, right bottom panel).

ACA infarction [4–6] (fig. 2). The most prevalent symptom of ACA territory infarction is contralateral hemiparesis or monoparesis, usually affecting the leg predominantly. Of the 100 patients with isolated ACA infarction reported by Kang and Kim [5], 91 showed motor deficits: hemiparesis in 70, leg monoparesis in 18, and paraparesis in 3. Leg weakness was dominant in 58 of these 91 patients (64%). Of the 48 patients in the study by Kumral et al. [4], 46 (96%) showed motor deficits, and all but 1 of these had leg weakness. In our cohort involving 42 patients with isolated ACA infarction, the median 'motor leg' subscore of the admission National Institutes of Health Stroke Scale on the weaker side was 2.5, while the median 'motor arm' subscore on the weaker side was 1 [6]. Predominant leg weakness is attributed to damage in the paracentral lobule. In contrast, weakness of the arm and face contralaterally to the ACA infarction is associated with involvement of Heubner's artery and the medial striate arteries. Paraparesis is caused by bilateral ACA infarction, which is often associated with absence or hypoplasia of the A1 segment. A sensory deficit is usually associated with motor weakness and predominantly involves the leg.

The second most common symptom among the 100 patients reported by Kang and Kim [5] was hypobulia (abulia) in 43. Lesions of the corpus callosum and cingulate gyrus are the major culprits. When such lesions are bilateral, hypobulia can occur more frequently. A typical symptom is 'akinetic mutism': patients may open their eyes and seem alert, and brief movement, speech, or even agitation may follow powerful stimuli, but they are otherwise indifferent, detached, frozen, and apathetic [8].

Several behavioral disorders can present as callosal disconnection signs. The grasp reflex, clenching the fingers to tactile stimulation of the palm, is a well-known sign. Patients grasp objects used for stimulation more firmly when an examiner tries to remove them (instinctive grasp reaction, forced grasping). Some patients have difficulty with bimanual tasks. In particular, the 'alien hand sign' occurs when an upper limb performs complex motor activities outside of volitional control. 'Diagnostic dyspraxia' is defined as abnormal and conflicting motor behavior of the left hand activated by voluntary movements of the right hand [9]. Other behavioral disorders include compulsive manipulation of tools and gait apraxia.

Several patterns of speech dysfunction can occur. In particular, aphasia is often transcortical and transient [4–6]. A lesion involving the left supplementary motor area is the major culprit for aphasic patients with ACA infarction [8]. Urinary incontinence developed in around 30% of all patients with ACA infarction in the studies by both Kumral et al. [4] and Kang and Kim [5]. Although headache has not been regarded as a typical symptom of ACA infarction, 13 of 42 patients (31%) in our series felt headache at stroke onset; 11 of these had a non-throbbing headache. This high frequency seems to be partly due to the high prevalence of ACA dissection in our patients. At 3 months, all patients reported by Kumral et al. [4] had survived. Of the 34 patients in our series who were completely independent prior to stroke, corresponding to a modified Rankin scale score of 0–1, 18 (53%) had a score of 0–1 again, and 5 patients (15%) had a score of 2 (functionally independent) at discharge from the acute hospital [6].

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Anterior Choroidal Artery Territory Infarction

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Abstract

The anterior choroidal artery (AChA) originates from the posterior wall of the internal carotid distal to the posterior communicating artery and proximal to the intracerebral carotid bifurcation. This thin artery is rarely the cause of aneurysm and only accounts for 2–5% of all aneurysms. Even though the AChA territory shows large variations among individuals, it supplies crucial motor and sensory structures, such as the internal capsule, optic tract, the posterior limb of the internal capsule, the cerebral peduncle, and the choroid plexus.

The classic clinical picture described for the first time in 1925 by Foix et al. [1] features, in its complete form, the triad of hemiparesis, hemianesthesia, and hemianopia. The absence of a cognitive deficit classically permits the differential diagnosis from cortical and subcortical lesions. Magnetic resonance imaging (MRI) of an anterior choroidal artery (AChA) infarct may not only play a diagnostic role but may also significantly contribute to the prognostic evaluation in AChA stroke patients.

Anatomy

The AChA commonly originates from the posterior wall of the internal carotid artery (fig. 1) 2–5 mm distal to the posterior communicating artery and 2–5 mm proximal to the carotid bifurcation [2, 3]. Occasionally it has been found to arise from the intracerebral carotid bifurcation or from the posterior communicating artery. The prevalence of duplication of the AChA remains controversial and many authors consider it a rarity. Of interest are the results of a recent neurosurgical series on AChA variations in 130 patients that reported that AChA may be found as a single (84.6%), double (13%) or as a triple branch (2.4%) at the ICA's origin. The course of the AChA can be divided into two segments – cisternal and intraventricular. The length of the cisternal segment ranges from 15 to 35 mm (mean 26 mm). In this segment the AChA has a complex relationship to the optic tract, which changes along its course. At its origin the AChA is located lateral to the optic tract, then it curves medially to the inferomedial surface, to curve again laterally running along the lateral aspect of the optic tract to reach the lateral geniculate body. The AChA then passes through the choroidal fissure to reach the choroid plexus of the temporal horn. The terms *plexal point* or *ventral choroidal point* have been proposed to describe the point of entry of the AChA into the lateral ventricle at the choroidal fissure [3]. The artery passes over the medial surface of the temporal horn, curving around the atrium to the floor of the body of the lateral ventricle. Within the

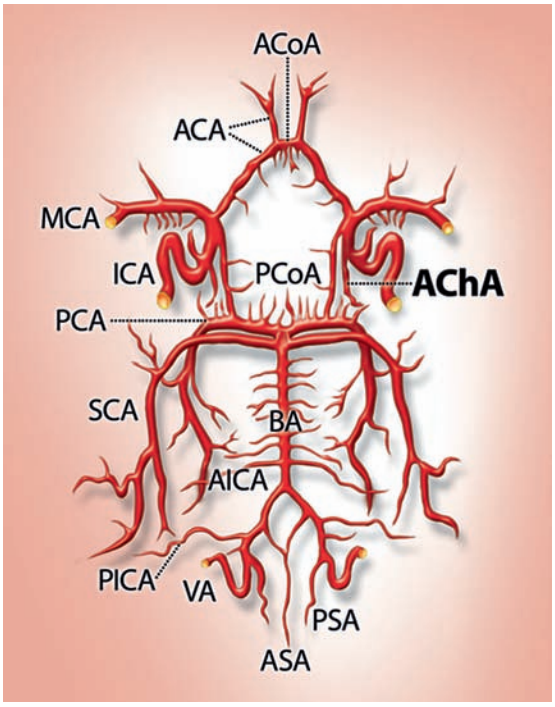

Fig. 1. AChA originating from the posterior wall of the internal carotid artery.

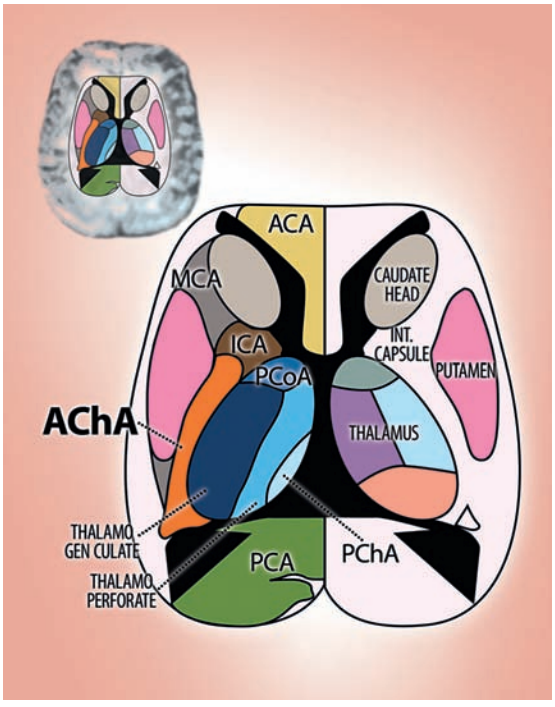

Fig. 2. Extent and boundaries of the AChA territory – the most reported supply areas are shown.

collateral trigone the AChA anastomoses with the posterior choroid artery [3]. The extent and the boundaries of the AChA territory are still being debated in the literature. The most reported supply areas include the optic tract, the uncus, the lateral part of the geniculate body, the posterior two-thirds of the posterior limbs of the internal capsule (fig. 2, 3), optic radiation, and the choroid plexus on the lateral ventricle [4]. Other territories, such as the lateral thalamic border and the medial part of the lentiform nucleus, are still subject to debate, although the most controversial territory is the posterior paraventricular territory. Despite its small size (0.5–2.0 mm), the AChA has perforating branches (between 2 and 9 AChA perforators with a diameter that varies from 90 to 600 μm) that have been identified in microdissection studies [5].

Epidemiology and Etiopathogenesis

Data on the epidemiology of AChA infarcts are scarce in the literature, as many publications are heterogeneous case studies and other investigations are not limited to the AChA territory infarcts. The prevalence of AChA strokes ranges from 2.9 to 11% [5] among patients with acute ischemic stroke. In a recent study [6] the prevalence of AChA infarct in 1,350 patients was 8.3%. The etiopathogenesis is heartily debated too: traditionally, AChA infarcts have been considered lacunar infarcts because of the small artery diameter, small vessel disease, large vessel disease, cardioembolic, or other determined or undetermined causes that have been considered too.

Ois et al. [6] studied AChA infarction in a prospective series of 1,350 patients with acute ischemic stroke. They found that compared to

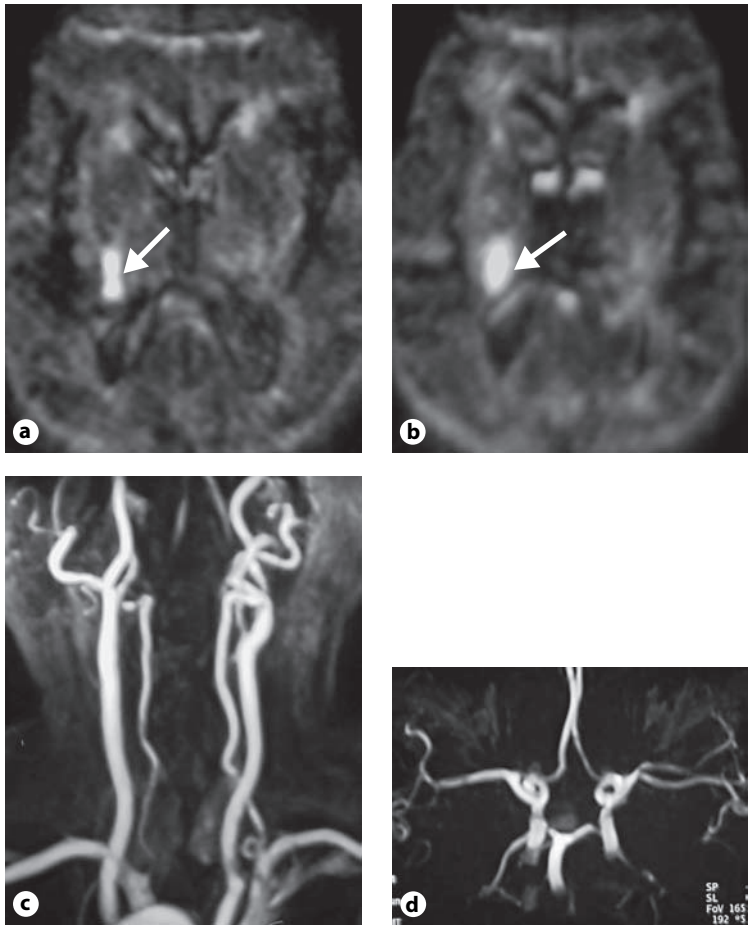

Fig. 3. Diffusion-weighted images of a patient with pure AChA infarction. Damaged areas show restricted diffusivity in the posterior limb of the internal capsule and the retrolenticular part of the internal capsule (**a**, arrow) with extension into the lateral thalamus (**b**, arrow). A 3D-TOF MR angiographic sequence with 3D MIP reconstruction demonstrates normal representation of supra-aortic vessels (**c**) and a parietal irregular representation of the carotid intrapetrous tract (**d**) suggestive of atherosclerosis.

hemispheric infarcts, AChA stroke patients were younger, more often male and diabetic, and less likely to be pretreated with antithrombotic therapy than hemispheric stroke patients. The same authors observed that AChA infarcts were less associated with embolic sources, and showed a higher risk of progression but a lower risk of recurrence or mortality than hemispheric infarcts. AChA infarct patients had a lower presence of severe arterial stenosis and cardioembolic sources than hemispheric infarcts patients, but a higher presence of severe arterial stenosis than patients with deep infarcts. A previous comprehensive work on the presumed pathogenesis of AChA infarcts investigated the pathogenesis of AChA infarcts according to the infarct size, using CT scans to measure small (<20 mm) and large (≥20 mm) lesions. The authors observed no differences between large AChA infarcts and hemispheric infarcts, either with respect to vascular risk factors or to potential underlying stroke causes, which led to the conclusion that most such infarcts are caused by large artery thromboembolism or cardiac embolism. Moreover, the authors observed that compared to small deep strokes in other territories, AChA infarcts <20 mm were more likely to be due to carotid stenosis and less to cardioembolism.

Clinical Manifestation

In 1925, Foix et al. [1] were the first to describe the AChA syndrome, which is quite rare in its complete form. The different patient series published to date all conclude that the motor deficit is by far the most frequent of the classically described triad, present in 87–100% of cases. It is caused by the interruption of the corticospinal fibers which descend in the posterior limb of the internal capsule and the cerebral peduncle. The motor deficit often evolves into undulating hemipareses, which sometimes progress to high-grade hemiparesis or hemiplegia but may also completely regress, depending on the integrity of the corticospinal tracts, as recently demonstrated by MRI diffusion tensor imaging studies [7]. The sensory deficit is highly variable and less frequent: reported rates in the literature range between 33 and 81%, visual deficits rates are between 0 and 42% and are often transient because of the rich collateral circulation. Pure visual disturbances as a clinical manifestation of AChA infarcts are extremely rare with only 3 cases reported [8]. Aphasia, if stroke is in the dominant hemisphere, confused state and other cortical signs are less frequent [6]. When present, neuropsychological disturbances may be due to the disconnection phenomenon caused by ischemic involvement of reticuloparietal connections (neglect) and/or reticuloanterior frontal connection (dysphasia) [9].

Imaging: Angiographic Findings

The AChA is not always visible on conventional angiograms, either because of its small diameter or because it is obscured by branches of the middle cerebral artery. In the literature, the frequency of angiographic visualization of this artery has been reported to be between 71 and 98% [10]. Some of the branches of the AChA can be identified on lateral angiograms. In the proximal half of the cisternal segment, ascending branches that course into the region of the globus pallidus and internal capsule are seen frequently. More posteriorly, small descending branches to the uncus may be noted. In the terminal portion of the cisternal segment, additional ascending branches that supply the region of the lateral geniculate body, posterior limb of the internal capsule, and retrolenticular area may be identified. Angiographic identification of the uncal artery and of perforating branches has been reported in 36 and 47% of cases, respectively [2, 3]. On lateral angiograms, the plexal point, where the artery enters the choroid plexus, is at a distance of 18–26 mm from the origin of the AChA. This important angiographic landmark is usually characterized by a steep downward course of a few millimeters, followed by a sharp posterior turn, marking the point of entry.

MRI of the AChA

MRI using a 3D-TOF MR angiographic sequence allows identification of the AChA with certainty in 95% of cases. This compares well with the rates of identification reported in studies using conventional angiography. MR angiography thus represents a useful, noninvasive alternative for screening the AChA [11]. Visualization of the AChA may be clinically important if an involvement of the artery is suspected in cases of infarctions, intracranial aneurysms, AVMs, or intracranial tumors. The anatomic features that help to identify the artery on the MR angiographic source images are (1) its typical point of origin from the posterior wall of the internal carotid distal to the PComA and proximal to the intracerebral carotid bifurcation, and (2) its characteristic posterior course, especially when it runs along the medial aspect of the uncus to curve laterally along the medial aspect of the temporal lobe (ambient gyrus) through the ambient cistern to the choroidal fissure. In general, identification of the AChA is easier using the 3D-TOF than the 3D- CISS sequence, most probably because of the high signal of the arteries in the former as compared with the latter sequence. Even though the 3D-CISS sequence is only helpful when the structures to be identified

are surrounded by CSF, it may give additional information, especially if combined with MR angiography, such as visualizing fine structures located in the cisterns and realistic measure of the diameter of the AChA than the 3D-TOF sequence. Arteries are easily identified by their bright signal when using the 3D-TOF sequence. While the 3D-CISS sequence depicts the external contour of the AChA, the 3D-TOF sequence shows flow within the vessel. Thus, using both sequences, it may be possible to discriminate hypoplasia of the vessel from occlusion in suspected cases of infarction or vasculitis. MR angiography is not able to depict branches of the AChA, presumably because of their small diameter. However, when the AChA supplies tumors or AVMs, it usually enlarges. In these cases, identification of the artery by MRI is easier. Finally, AChA can be reliably identified using both a 3D-CISS sequence as well as source images of a 3D-TOF sequence. MRI is a useful noninvasive alternative for screening the AChA and can be used to assess and follow up AChA-related disorders [11]. MRI may also have a prognostic role: Nelles et al. [7] suggested that diffusion tensor tractography may explain the resulting motor dysfunction in patients with AChA infarcts with more notably decreased fractional anisotropy being an indicator for an unfavorable outcome.

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Posterior Cerebral Artery Territory Infarctions

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Abstract

Infarctions in the territory of the posterior cerebral artery (PCA) occur in about 5–10% of all ischemic strokes. The PCA can be divided into 'deep' (P1 and P2 segments) and 'superficial' (P3 and P4) segments. Occlusion of paramedian perforating arteries arising from P1 causes rostral midbrain infarction with or without thalamic lesion. The classical clinical triad after thalamomesencephalic infarcts is hypersomnolence, cognitive deficits and vertical oculomotor paresis. Two main arterial groups arise from P2: infarction in the territory of the thalamogeniculate arteries causes severe contralateral hypesthesia and ataxia, whereas infarction in the territory of the posterior choroidal arteries results in sectoranopia with involvement of the lateral geniculate body. After superficial PCA infarcts, visual field defects and somatosensory deficits are the most frequent signs. Additionally, disorders of reading may be seen after unilateral left infarction and disorientation for place and visual neglect after right lesion. After bilateral PCA infarcts, amnesia, cortical blindness (the patient cannot see but pretend he can) may occur. Acute thrombolysis is as useful after PCA infarctions as after anterior circulation strokes. Mortality after PCA strokes is low, but long-term behavioral and cognitive deficits are underestimated.

Because of its strategic location, the posterior cerebral artery (PCA) plays a major role in the blood supply of the brain. Unlike any other brain artery, the PCA and its branches supply a large territory derived from mesencephalic, diencephalic and telencephalic embryologic structures. It is therefore not surprising that infarcts of the PCA cause a broad range of clinical signs ranging from vertical oculomotor paresis after midbrain infarct to peculiar cognitive syndromes after thalamic or temporo-occipital strokes. For the last 30 years and the development of brain CT and later MRI, there have been extensive reports of the clinical manifestations after PCA infarcts which, overall, account for about 5–10% of all ischemic strokes [1, 2]. However, because the resolution of brain imaging continuously improves especially regarding the posterior cerebral circulation, a more accurate anatomoclinical correlation after PCA stroke is now possible. Furthermore, new studies have recently refined the efficacy of thrombolysis after PCA strokes [3, 4].

Anatomy

There is one PCA for each cerebral hemisphere arising from the top of the basilar artery in 70% of the patients. In 20% of the cases, the PCA arise from the posterior communicating artery (PComA) and in 10% from a mixed origin. The PCA may be divided into 4 segments. P1 from the top of the basilar artery to the PComA, P2 after the PComA. P3 and P4 segments refer to the

distal segments with cortical branches. The PCA can be divided into deep (P1 and P2) and superficial (P3 and P4) segments. Infarction limited to the deep or superficial segments account each for 25% of PCA infarctions, whereas combined deep and superficial infarcts occur in 50% of them [5].

Etiology

The etiology of PCA infarcts is mostly embolic. Embolism may originate from atheromatous or dissected vertebral arteries, from the aorta or from the heart [6]. The 'top of the basilar syndrome' resulting in occlusion of the top of the basilar artery and both proximal PCA is typically of cardioembolic origin [7]. To note, however, infarctions in the territory of two PCA branches, the thalamogeniculate and the posterior choroidal arteries are mainly caused by small-vessel disease [8]. Intrinsic atheromatous disease as a cause PCA infarction is rare but possibly more frequent in the Asian population. Migraine is more frequently a cause of PCA than anterior circulation strokes [9].

Clinical Manifestations

P1 Segment. Small perforating arteries arise at the distal basilar bifurcation or from P1 and supply the rostral midbrain. These are similar to the other perforating paramedian arteries found at the bulbar, pontine and midbrain level. Infarctions of the parmamedian perforating arteries result in various clinical syndrome including ipsilateral third nerve palsy, Horner syndrome, contralateral hemiparesis and hemiataxia. Skew deviation and vertical oculomotor paresis is caused by lesions of the nuclei of Cajal and Darkschewitsch and/or interruption of the corticomesencephalic and mesencephalic tracts responsible for vertical eye movements control. The paramedian thalamic artery, a perforating paramedian branch from P1, supplies the medial thalami and the walls of the third ventricle. In one third of the hemisphere, one paramedian pedicle supplies both thalami [10]. Patients with infarction of the paramedian part of the thalamus classical present a triad with (1) hypersomnia by involvement of the dorsomedial and intralaminar nucleus, (2) cognitive dysfunction, mainly amnesia and transcortical motor aphasia with left lesion following lesion of the dorsomedial nucleus, and (3) vertical oculomotor paresis [11, 12]. Not infrequently, thalamomesencephalic perforating arteries exist resulting in a combination of rostral midbrain and thalamic signs when occluded [13].

P2 Segment. Although less frequently than from P1, perforating arteries to the midbrain may also arise from P2. More distally, the thalamogeniculate arteries consisting of 3–7 arteries represent the first major arterial group arising from P2 and correspond to the short circumferential arteries. They travel between the medial and lateral geniculate bodies and follow the inferolateral thalamus to supply its lateral and ventrolateral regions. As a consequence, occlusion of the thalamogeniculate arteries results in severe contralateral hemihypesthesia by involvement of the sensory relays in the ventroposterolateral and ventroposteromedial nuclei. Hemiataxia is also a frequent sign due to lesion of the ventrolateral nucleus. Because the thalamogeniculate arteries do no supply the internal capsule, contralateral hemiparesia is, when present, only mild and transient [14]. Delayed and persisting pain of the contralateral hemibody, referred as the Déjerine-Roussy syndrome, may occur within a week or months after a stroke. Next to the thalamogeniculate group, the posterior choroidal artery corresponds to the long circumferential artery and can be divided into a medial and lateral branches. Infarction of the posterior choroidal artery affects the lateral geniculate body, the pulvinar, and parts of the hippocampus and parahippocampal gyrus. The most suggestive sign of stroke in this territory is homonymous horizontal sectoranopia [15].

P3 and P4 Segments. Two inferior temporal arteries (the anterior and the posterior) arise from P3 (more rarely from the distal P2) supplying the medial part of the temporal lobe. From P4, three

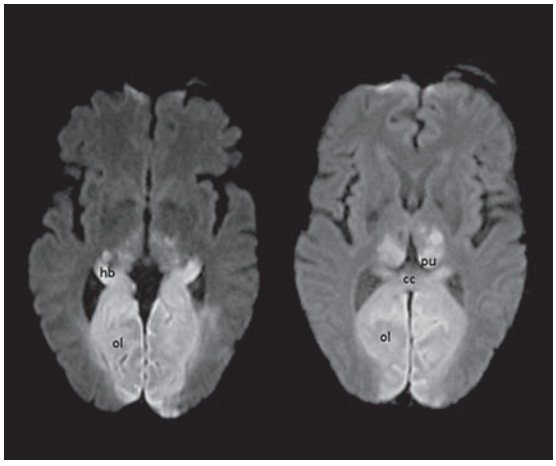

Fig. 1. Bilateral complete infarction of the deep and superficial segments of the PCA in a 64-year-old man presenting with acute coma. ol = Occipital lobe; hb = hippocampus body; pu = pulvinar; cc = corpus callosum.

main branches arise: the occiptotemporal, the calcarine and the occipitoparietal arteries. Clinical syndromes resulting from occlusion of both P3 and P4 will be discussed in the same section.

The lower part of the visual radiations is supplied by the PCA or its branches, from the lateral geniculate body to the occipital cortex, whereas its upper part is supplied by branches of the MCA. As a rule, the closer to the cortex the infarction is, the more congruent is the defect of the visual field. Depending on the location of the infarction, typical defects of the visual field are encountered. A homonymous lateral hemianopia sparing a temporal crescent is found when the inferior lip of the calcarine cortex is spared. Homonymous lateral hemianopia sparing the macula is not uncommon after occipital strokes since the blood supply to the macula may originate from the posterior MCA. Visual perseveration (palinopia) and visual distortions, such as micropsia and more rarely macropsia, can be described with distal PCA stroke affecting the occipital lobe in association with severe hemianopia.

Somatosensory sensory deficits are frequently seen after acute cortical PCA strokes occurring secondary to the interruption of the thalamic projection to the sensory cortex, itself supplied by branches of the MCA territory [16].

Left unilateral PCA: Pure alexia (alexia without agraphia) is probably the most characteristic sign of PCA strokes occurring after simultaneous infarction of the posterior section of the splenium and the left occipital cortex disconnecting the right occipital cortex to the left dominant hemisphere [17]. The association of disorders of writing and reading, i.e. alexia with agraphia, is classically found after lesion of the angular cortex of the inferior parietal lobule supplied by the MCA. Hemidyslexia, or paralexia, is defined as misreading of the right hand end of longer word is another disorder or reading described after left occipital lesion. Color anomia and agnosia are referred, respectively, to the inability to name and identify colors. Aphasia after distal PCA strokes is characterized by fluent speech, paraphasic errors and jargon. However, even when comprehension is severely impaired, patients may be able to repeat words, fulfilling the definition of transcortical sensory aphasia.

Right unilateral PCA: Left visual neglect is less frequently found than after posterior MCA infarct but may occur with large right PCA strokes. Prosopagnosia is defined by the difficulty to identify a familiar face. There is conflicting evidence to determine whether a unilateral right temporal stroke is sufficient to cause prosopagnosia or whether a bilateral infarction is needed. Constructional apraxia (difficulties for drawing) and topographic disorientation reflect the visuospatial functions of the right posterior hemisphere. Recently, cortical PCA strokes with or without involvement of thalamic structures were reported to induce aggressive behavior. This pattern seems to be more frequent after right PCA lesions but may also occur after a left lesion [18].

Bilateral PCA: Amnesia is only mild and transient after involvement of a unilateral lesion of the hippocampus or limbic cortex. Bilateral lesions are necessary to cause severe or persistent amnesia. Bilateral PCA infarctions including its superficial segments may cause cortical blindness.

The patients presenting with this syndrome cannot see but pretend they can [19].

Management and Outcome

Regarding acute thrombolysis, there is no difference in terms of efficacy and side effects between supratentorial PCA and anterior circulation infarcts, reflecting the importance of an 'aggressive' acute treatment of PCA strokes [3]. Thrombolytic treatment should be started without delay. A recent study did not find any significant difference between intra-arterial and intravenous thrombolysis for PCA strokes [4]. Rarely a malignant evolution of PCA strokes may occur leading to brainstem compression and death [20]. Overall, however, the risk of death after PCA strokes is only 5% and even less when midbrain and thalamic structures are spared. By far, visual field defects are the most common long-term deficits, whereas sensory abnormalities and motor weakness less frequently persist after the acute phase. The initial evolution may be wrongly reassuring with patients recovering well from hemiparesis but showing persistent behavioral and cognitive deficits [16]. In the future, further studies have to focus on this specific aspect to understand the connection of infarcted PCA territories to other brain structures.

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Thalamic Infarcts and Hemorrhages

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Abstract

The anatomy and supply of thalamic arteries are briefly described here. Thalamic infarcts and small-size hemorrhages are classified according to their sites: (1) posterolateral, (2) anterolateral, (3) medial, and (4) dorsal. (1) Posterolateral hemorrhages or lateral thalamic infarcts are usually characterized by severe motor impairment and sensory loss. Transient reduced consciousness, vertical-gaze abnormalities, and small fixed pupils may be evidenced. (2) Patients with anterolateral hemorrhages or tuberothalamic artery infarcts present frontal-type neuropsychological symptoms associated with mild hemiparesis and hemihypesthesia. (3) Medially located hemorrhages or paramedian artery infarcts have decreased levels of consciousness, vertical- and horizontal-gaze abnormalities, amnesia, and abulia. (4) Dorsal hemorrhages or posterior choroidal artery infarcts present with minimal transient hemiparesis and hemihypesthesia; apraxia, aphasia, and amnesia have also been described.

The thalamus is a subcortical structure which includes gray-matter nuclei. The right and left thalamus are located at the top of the midbrain, which have a strategic function since they are a major relay between the cerebral cortex and brainstem region. The anatomy and vascularization of this region are intricate; for this reason, hemorrhagic and ischemic stroke present as many different thalamic syndromes.

The thalamus receives most of its blood supply from four arteries: (1) inferolateral arteries, (2) tuberothalamic artery, (3) paramedian arteries, and (4) posterior choroidal arteries [1–3] (fig. 1). These arteries originate from the basilar artery bifurcation, the posterior communicating artery, and the proximal portions of the posterior cerebral arteries (PCA). The thalamic arteries differ between subjects regarding parent vessel origin, number, location and supply zone [2].

Thalamic Infarcts

Infarcts in the Territory of the Tuberothalamic Artery. The tuberothalamic artery (also known as polar, anterior thalamoperforating, anterior internal optic or premammillary pedicle) usually arises from the middle third of the posterior communicating artery. Infarct in the supply zone of this artery often presents as cognitive and behavioral disturbances. Left hemisphere lesions trigger memory, language deficit and acalculia. Memory dysfunction presents as difficulties in recalling and acquisition, either visual or verbal information, together with time disorientation [4]. The last symptom, which can be associated with 'chronotaraxis' (e.g. loss of time sense), is provoked by dorsomedial nucleus disruption [5]. Amnestic syndrome is related to both the disruption of the

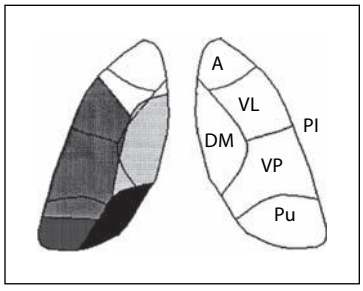

Fig. 1. Vascular territory of the thalamus (reproduced with permission [25]). Black area = posterolateral choroidal artery; dark gray area = posteromedial choroidal artery; medium gray area = inferolateral arteries; light gray area = paramedian thalamic artery; white area = tuberothalamic artery. A = Anterior thalamic nucleus; DM = dorsomedian thalamic nucleus; VL = ventral lateral thalamic nucleus; VP = ventral posterior thalamic nucleus; Pu = pulvinar; PI = posterior limb of internal capsule.

mammillothalamic tract that disconnects the anterior thalamic nuclei from hippocampal formation and the amygdalothalamic projections which disconnect amygdala from anterior nuclei [6]. Language symptoms have been consistently described throughout the literature and have been defined as 'thalamic aphasia', which is characterized by anomia with decreased fluency, comprehension impairment, and fluent paraphasic speech lacking meaningful content [7, 8]. Naming can show a dichotomy animate/inanimate when the stimuli were presented visually but not when the stimuli were auditory [9]. Semantic and phonemic paraphasia are common, with occasional neologisms and perseveration. Oral reading is usually relatively preserved, reading comprehension is markedly limited, while repetition is often preserved. Right-side infarcts are known to cause visual memory impairment and mild cognitive deficits [7]. These patients exhibit specific behaviors such as perseverations and superimpositions of unrelated information, apathy, abulia [10] and anosoagnosia [8]. Bilateral infarcts of the tuberothalamic arteries can cause severe and permanent abulia and amnestic disturbances.

Infarcts in the Territory of the Paramedian Arteries. The paramedian arteries (also called the thalamic-subthalamic, deep interpeduncular profunda, posterior internal optic arteries, or thalamoperforating pedicle) arise from the proximal P1 peduncular segment of the PCA. Patients with unilateral infarcts of the paramedian arteries are characterized by decreased levels of consciousness, cognitive and behavioral disturbances. The same features together with vertical-gaze abnormalities are present in bilateral infarcts [11]. These patients exhibit decreased and fluctuating levels of consciousness in the early phase followed by confusion, agitation, aggression, and apathy, which may become irreversible. Bilateral infarcts can lead to lethargia and even coma. The vigilance impairment is thought to be caused by a disruption of the interlaminar nuclei and the rostral midbrain reticular formation. In these patients, vertical-gaze function is impaired: up-gaze palsy or combined up- and down-gaze palsy are often present [12], as well as skew deviation [13]. Pure down-gaze palsy is found only in cases of bilateral infarcts. Horizontal-gaze dysfunction is much less common. Disconjugate abnormalities, such as acute esotropia, loss of convergence, pseudo-sixth nerve palsies, bilateral internuclear ophthalmoplegia, miosis, and intolerance to bright light have been described [14].

Following the acute phase, cognitive symptoms including amnesia, disorientation, new learning impairment as well as temporary neglect become more prominent [15]. Abnormal movements, such as asterixis, tremor, or dystonia, may occur in the contralateral limbs, usually after a delay of several weeks [16]. Blepharospasm has also been reported [17]. Bilateral paramedian infarcts may be provoked by the artery of Percheron. In this uncommon anatomic variant, a solitary trunk originates from PCA and provides arterial supply to bilateral paramedian thalami and the rostral midbrain [18]. This occlusion causes severe cognitive deficits, which can be long-lasting causing

a clinical picture called 'thalamic dementia'; this pattern may often be difficult to distinguish from primary psychiatric disorders, especially when neurologic dysfunction is lacking [10, 19]; akinetic mutism has also been described [20]. Behavioral symptoms including utilization behavior, disinhibition, personality changes and abulia are common [10].

Inferolateral Arteries Infarct. The inferolateral (also called thalamogeniculate) arteries are a pedicle of 6–10 arteries arising from the P2 branch of the PCA. Their occlusion present with three common clinical manifestations: (1) pure sensory stroke, (2) sensorimotor stroke, and (3) the 'classical' thalamic syndrome. Patients with pure sensitive syndromes, caused by ventromedial and ventrolateral nuclei infarction, experience severe paresthesias or numbness associated with hemisensory deficit [21]. Sensory deficit may affect all sensory modalities but can also be dissociated with sparing of touch, temperature, and pin sense [7]. Moreover, sensory deficit may be transitory or permanent or change in a delayed painful syndrome of the affected area – the *'anesthésie douloureuse'* [11, 22].

Sensorimotor stroke, caused by infarct of the ventrolateral nuclei and the adjacent posterior limb of the internal capsule, presents with the above-described sensory disturbances together with motor abnormalities on the same side (e.g. hemiparesis, increased tendon reflexes, and Babinski sign) [23].

The more extensive form of lateral thalamic infarction was originally described by Dejerine and Roussy in 1906 as 'the thalamic syndrome' [22]. This syndrome is characterized by abnormal movement patterns resulting from interruption of extrapyramidal and cerebellar tracts that synapse in the lateral thalamus in addition to the clinical manifestations of pure sensory and sensorimotor strokes. Cerebellar-type hemiataxia, oscillations, hypermetria, and dysdiadochokinesia have been described [24]. Corea, dystonia, athetosis and action tremor has also been described [25]. Patients may also experience a predominant inability to stand and walk called 'thalamic astasia' [26]. Patients present also with alteration of their sense of body verticality (e.g. they perceive their body as upright when it is actually tilted nearly 20 degrees to the ipsilesional side). This is called 'Pusher syndrome' and it is associated with posterior thalamic stroke [27]. Other abnormal movements, such as hemidystonia and hand jerks are often associated with severe sensory loss and ataxia. The hand is often flexed and pronated, with the thumb buried beneath the other fingers – *'la main thalamique'* [24, 28]. Cognition ability and behavior are usually preserved in patients with lateral thalamic infarcts, although executive dysfunction may be present and lead to severe long-term disability [10]. Auditory illusions have been associated with right medial geniculate body disruption [29]. Finally, anosoagnosia in right hemisphere lesions has also been described [8].

Infarcts in the Territory of the Posterior Choroidal Artery. The medial and lateral posterior choroidal arteries originate from the P2 segment of the PCA. The most common presenting symptoms of posterior choroidal artery are visual-field defects including upper or lower quadrantanopia, horizontal wedge-shaped or tubular sectoranopias, which are related to lateral geniculate body disruption [30, 31].

Thalamic Hemorrhages

Symptoms of thalamic hemorrhages are related with the size and site of the bleeding. Small hemorrhages are <2 cm, by definition, and present with symptoms similar to the above-described thalamic syndromes related to ischemic events. In addition, large thalamic hemorrhages are >2 cm in diameter and have overlapping clinical syndromes. Common features of small and large thalamic hemorrhages include rapid onset, unpredictable impairment of consciousness, and a

relatively good prognosis, compared to hemorrhages located in the pons and basal ganglia [1, 32].

Large Thalamic Hemorrhages. Large thalamic hemorrhages typically present with rapidly progressive motor deficits, sensory loss, vertical-gaze abnormalities, and pupil abnormalities [33, 34]. Contrary to infarcts, thalamic hemorrhages have motor deficits that are usually more evident than sensory abnormalities [34]. Sensory ataxic hemiparesis with incoordination of the contralateral limbs and severe impairment of proprioceptive sensation have also been described [35]. A decreased level of consciousness is frequent. Neuropsychological disturbances are also commonly observed; the classical picture includes mild fluent aphasia, with paraphasic errors and dysnomia, but comprehension and repetition abilities are usually preserved [36].

Small Thalamic Hemorrhages. The deficits related to small thalamic hemorrhages are shared by single artery infarcts described in the above section entitled 'Thalamic Infarcts'.

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Caudate Infarcts and Hemorrhages

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Abstract

The caudate nucleus (CN) is composed of a head, body and tail. The head of the CN contributes to forming the floor of the lateral ventricle frontal horn. Moreover, the head, which is medially separated by the septum pellucidum extends beyond the anterior part of the thalamus, stroking the telencephalic cortex. The superior part of the head is covered by the knee of the corpus callosum, while the inferior part is below the thalamus and lenticular nucleus, which delimits the internal capsule. CN strokes are classified into hemorrhagic and ischemic. The clinical presentation of CN hemorrhage is often characterized by a clinical presentation mimicking subarachnoid hemorrhage, while clinical features of both ischemic and hemorrhagic strokes included behavioral abnormalities dysarthria, movement disorders, language disturbances and memory loss. Most studies to date that have examined vascular CN pathologies have evidenced good outcomes.

Anatomy

The caudate nucleus (CN) is composed of a head, body and tail. The head of the CN contributes to forming the floor of the lateral ventricle frontal horn. Moreover, the head, which is medially separated by the septum pellucidum, extends beyond the anterior part of the thalamus, stroking the telencephalic cortex. The superior part of the head is covered by the knee of the corpus callosum, while the inferior part is underneath the thalamus and lenticular nucleus, which delimits the internal capsule. The superior part of the body contributes to the formation of the frontal horn of the lateral ventricle, whereas its inferior part is attached to the internal capsule. Finally, the lateral part of the body is attached to the corona radiate, while the medial part is attached to the thalamus.

The tail, first travels to the thalamus and back, and then moves below the internal capsule, thereby delimiting the roof of the temporal horn of the lateral ventricle. Finally, the frontal part of the tail thins out and moves to the amygdaloid nucleus. Due to anatomic continuity with the lateral ventricle, internal capsule, lenticular nucleus and thalamus, it is difficult to define anatomic localizations of CN pathologies.

Vascular supply to the CN relies upon deep perforators from diverse arteries, the two principal ones being the anterior (ACA) and middle cerebral arteries (MCA). ACA supplies a part of the CN head: Heubner's artery is responsible for supplying the inferior part of the CN head as well as the adjacent anterior limb of the internal capsule and the subfrontal white matter. From Heubner's artery, on average four deep perforators arise, having diameters similar to those of the lenticulostriate branches of MCA [1, 2]. Furthermore, direct penetrating arteries

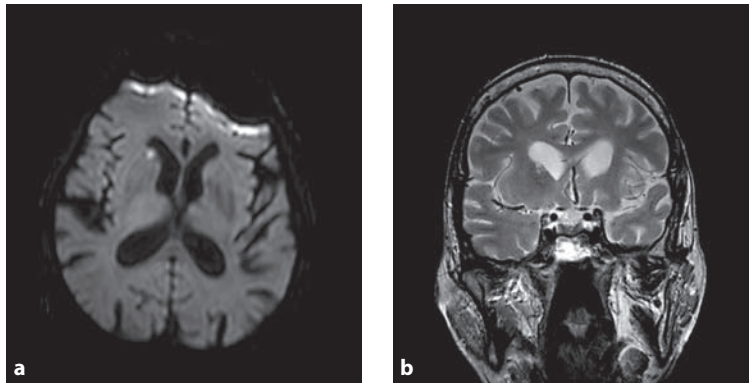

Fig. 1. **a** Right CN infarct in diffusion-weighted imaging. **b** Same infarct in T_2.

from the ACA supply the anterior portion of the CN head [2]. The medial lenticulostriate arteries originating from the proximal M1 portion of the MCA supply both a small portion of the lateral border of the caudate head and the adjacent internal capsule. The lateral lenticulostriate artery branches, from the mainstream MCA or its superior division branch, supply the largest portion of the CN head, as well as the adjacent internal capsule and the anterior half of the putamen The CN, due to its paraventricular location, is also perfused by ependymal arteries which flow outward from the ventricular surface into the cerebral parenchyma [3].

Main Causes of CN Strokes

CN strokes are classified into hemorrhagic and ischemic (fig. 1a, b). The main cause of caudate hemorrhage is hypertension, while other causes can include the rupture of internal carotid artery aneurysms [4], or the rupture of arteriovenous malformations. In the latter case, patient age tends to be much lower than in those with hypertension [5, 6], while another but less frequent cause has been reported to be Moyamoya disease [7, 8]. Finally, a single case of caudate hemorrhage, diagnosed as a complication of midodrine-induced supine hypertension, has been reported by Sandroni et al. [9].

Small vessel disease is the primary cause (59–66%) of ischemic stroke in CN, followed by cardioembolic etiology (20%), ipsilateral significant carotid stenosis and occlusion (8%). Furthermore, a single case of ischemic stroke involving the territory of Heubner's artery due to syphilitic vasculitis has been described [7].

Clinical Features

Lesion sizes, locations and involvements of the nearby structures define clinical presentations. Specifically, the clinical presentation of CN hemorrhage can be characterized as in subarachnoid hemorrhage by (1) headache, nausea and vomiting, neck stiffness, decreased level of consciousness, without neurological focal signs; (2) the above symptoms plus focal signs such as hemiparesis or aphasia, and (3) predominance of neuropsychological disturbances, disorientation, aphasia along with mental confusion without meningeal signs [10].

Stein et al. [3] have proposed an anatomically based classification: (1) symptoms and signs include vomiting, headache, neck stiffness, decreased level of consciousness, and behavioural change, which can mimic the presentation of subarachnoid hemorrhage, where blood is primarily localized to the head of the CN, and (2) symptoms and signs include gaze abnormalities and

hemiparesis, with or without sensory loss; both the anterior limb of the internal capsule and the body of the CN tend to be involved. Stein et al. [3] have described Horner's syndrome in 2 patients, where the hemorrhages had more inferior and lateral extensions.

Behavioral Abnormalities

These may occur as a result of a loss of function in the cortical zones, caused by a lack of striatal efferent projections from the CN [5]. Kumral et al. [5] have described a series of patients with abulia, having decreased spontaneous motor activity and prolonged latency in responding to stimuli; psychic akinesia with severe mental and affective stagnation and lack of initiative, while a second group exhibited restlessness, disinhibition, impulsivity and confusion, and a third group had affective symptoms with psychotic features. Mendez et al. [11] have reported that symptoms of the first group seemed to be caused by dorsolateral nucleus caudate lesions, while those of the second group, a minor involvement of the ventromedial part, and those in the third group, larger lesions of the dorsolateral region extending into the adjacent structures. Fuh et al. [8] described a series of patients where most experienced confusion and loss of interest, while only 1 patient was described as disinherited and inappropriate, without showing any clear distinctions between dorsal and ventral involvement on CT.

Dysarthria

Dysarthria has been commonly observed in patients with caudate vascular lesions. However, Kumral et al. [5] did not observe a side predominance among dysarthric patients (13/31), while they did report lesions limited to the CN in 2 patients and an involvement of the anterior limb of the internal capsule and anterior putamen in 8 others.

Movement Disorders

These have been described as ballistic, choreic or both. Delayed onset of abnormal movements and dystonia more than a decade after infantile stroke has been described [12]. A case of a CN bilateral lesion with bilateral movement disorders has also been reported [13, 14]. Kwak et al. [15] have reported on 2 juvenile stroke patients (12 and 22 years old) both having vascular lesions of the basal ganglia which also involved the head of the CN leading to hemidystonia together with tourettism.

Language Disturbances

Kumral et al. [5] have reported identical language impairments in 5 patients with infarcts of the left CN, among these, 3 patients had a non-fluent type of aphasia characterized by syntax errors, repetition impairment, stuttering, word-finding difficulty and preserved comprehension. Aphasia resolved in 2 weeks in all patients except for 1 having global aphasia. Stein et al. [3] have described aphasia onset in CN hemorrhage only after both lateral and frontal blood extension, while Pedrazzi et al. [10] have described a preponderance of semantic paraphasias.

Memory Impairment

Studies have documented a frequent involvement of memory in CN pathologies. In fact, Fuh et al. [8] have affirmed that memory either short term or long term was the most significantly impaired process in CN hemorrhages. These observations are in agreement with those described by Mendez et al. [11] where patients with caudate lesions showed impaired ability to initiate effective retrieval strategies. Stein et al. [3] described a patient with a possible involvement of other structures such as the thalamus presenting memory disorders. Kumral et al. [5] have reported that one third of left CN lesions presented verbal amnesia, while patients with right caudate lesions had

visual amnesia, suggesting the role of CN in the integration of visual and verbal memories.

Prognosis

Most studies to date that have examined vascular CN pathologies have evidenced good outcomes [3, 5, 10] with the exception of the Weisberg series [16], where a worse prognosis has been described. Specifically, Kumral et al. [5] have reported that 60% of patients with caudate infarct and 50% of those with CN hemorrhages recovered completely, even in the presence of hydrocephalus.

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Putaminal Hemorrhages

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Abstract

The putamen is a common site of hypertensive cerebral hemorrhage. Such hemorrhages show a large range of possible presentations – from enormous hemorrhages involving the white matter of the hemispheres and the ventricular system, to cases occurring without causing any symptoms or neurological signs. The symptoms of onset, the clinical evolution and the outcome are largely due to the magnitude of the initial blood extravasation. This chapter describes typical as well as rare clinical manifestations of putaminal hemorrhages.

Regional Vascular Anatomy

The putamen is the largest and most lateral part of the basal ganglia and is characterized by a high neuronal density as well as a rich vascularization from lenticulostriate arteries (LSa). The LSa originates from the anterior and middle cerebral arteries (fig. 1). The origin of the LSa is very variable and the scheme presented here has only an indicative value; among the anomalies of these arteries (fig. 2a, b) it deserves to be remembered that the origin of the lateral and medial LSa arise from a single trunk artery (artery of Charcot). The LSa are 'end vessels' of small diameter (about 100–400 μm) originating at a right angle from a large diameter vessel without the gradual stepdown in size that occurs in the distal cortical vessels. Their internal blood flow pressure may be very high. For this reason the LSa are particularly susceptible to damage from hypertension as their rupture can produce an intracerebral hemorrhage that is initially centered in the region. This manifestation may involve neighboring structures, like the internal capsule and other more distant white matter of the hemisphere, and may even rupture into the ventricular system. Due to their anatomical characteristics, the perforating vessels may be subject to intraluminal pressures much higher than those found in arterioles of similar size elsewhere in the brain [1, 2] and numerous histological alterations resulting from chronic hypertension may be seen, including microatheroma, lipohyalinosis, fibrinoid necrosis, and microaneurysm [1]. The morphological changes induced by hypertension can lead to a small-vessel occlusive phenomena as well as microaneurysm formations and thus explaining the frequent concurrence of lacunae and hemorrhage in the same patient.

Clinical Syndromes

The putamen is a common site of hypertensive cerebral hemorrhage; these hematomas account for 15–48% of cases of primary brain hemorrhage in the United States and Europe [3, 4], and 35–64% in Japan [5]. However, such hemorrhages show a large range of possible presentations: from enormous hemorrhages involving the white matter of

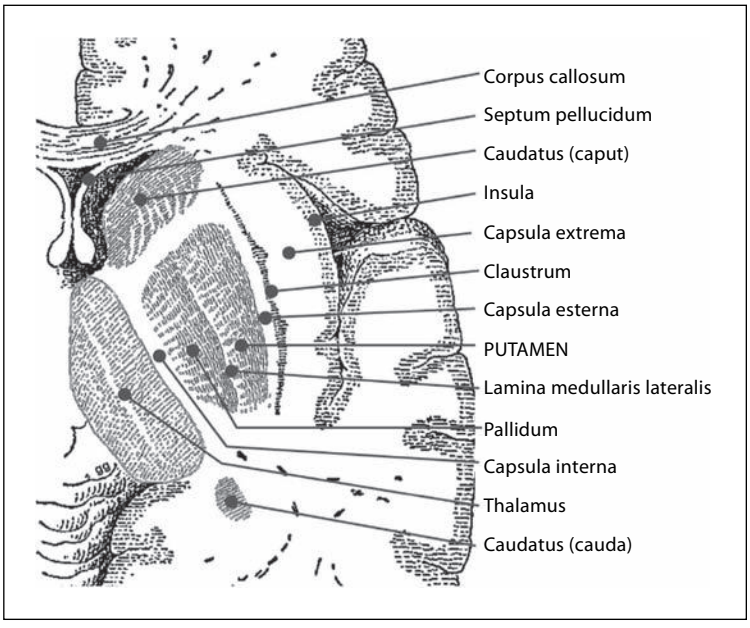

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Fig. 1. An axial section through the basal ganglia shows the relationships of the striatum with the system of the capsule, the caudate nucleus and thalamus.

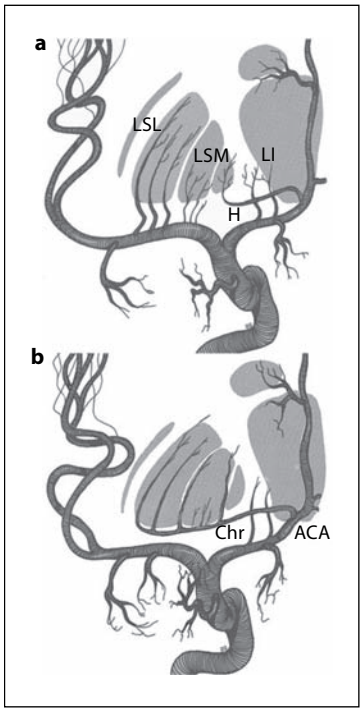

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Fig. 2. The origin of lenticulostriate arteries (LSa) is very variable (see text for details). **a** LSL = Lateral LSa; LSM = medial LSa; LI = internal LSa. **b** H = Artery of Heubner; Chr = artery of Charcot.

the hemispheres and the ventricular system, to cases occurring without causing any symptoms or neurological signs [6].

The symptoms of onset, the clinical evolution and the outcome are largely due to the magnitude of the initial blood extravasation. In the *massive or fulminant putaminal hemorrhage* a huge hematoma (often with a volume near to 100 cm^3) is usually accompanied by ventricular compression and intraventricular hemorrhage. Enlargement of the hematoma can be documented by serial CT studies. In these patients sudden development of neurological symptoms can occur, such as flaccid hemiparesis and hemisensory deficits, sometimes followed by rapid deterioration leading to coma within a few minutes or hours. Such patients may be found stuporous or comatose and frequently will vomit immediately after the onset of symptoms. They will present bilateral extensor plantar reflexes, ipsilateral dilated pupil or bilateral midriatic fixed pupils and Cheyne-Stokes or ataxic respiration, indicating the rapid development of brain herniation. The mortality rate for this can be extremely high [7].

Regarding the *classic putaminal hemorrhage,* the volume of the hematoma is more contained; in these cases the impairment of consciousness is mild to moderate but it usually appears with an onset of flaccid hemiplegia and a complete hemisensory deficit. If hemorrhage occurs near the anterior limb of the internal capsule, motor paresis is most often relatively mild and resolves in most cases; if the posterior limb is involved, severe hemiplegia with hemisensory impairment involving all modalities is more frequent.

Reported ocular manifestations consist of homonymous hemianopsia when the hematoma

extends posteriorly and involves the optic radiation, paralysis of conjugate gaze on the opposite side the lesion resulting in conjugate deviation of the eyes towards the affected site or a conjugate gaze deviation on the side of the lesion. Abnormalities of higher cortical functions may coexist, such as aphasia and unilateral spatial neglect [8]. Typically there is gradual worsening of these manifestations during the first hours, often accompanied by headache and vomiting.

In the *putaminal hemorrhage of the dominant lobe,* the development of *aphasic syndromes* is among the most serious deficiency to afflict patients. Patients with hematomas extending anteriorly tend to develop Broca-type aphasia, whereas hematomas extending posteriorly into the temporal isthmus tend to cause global or Wernicke aphasia. Thus, the presence or absence of aphasic syndrome, the type of aphasia that develops and the recovery from aphasia are jointly related to the volume of hematoma, the direction of hematoma extension and the residual organic damage of involved subcortical white matter.

In the *putaminal hemorrhage of the non-dominant lobe* disturbances of higher cortical functions such as unilateral spatial neglect apractognosia (disorder that consists of several apraxic syndromes stemming from an impairment of spatial perception), hemisomatognosia, anosognosia for hemiplegia motor impersistence and non-aphasic misnaming have been described [8]. Prominent inattention and neglect syndromes are seen in cases of vertical extension of the putaminal hematomas in non-dominant hemisphere [8]. In a few cases, *alloesthesia* may occur, a condition in which a sensory stimulus, given on one side of the body, is perceived as being on the opposite side [9].

With regard to mortality and functional recovery, if the hemorrhage is of moderate volume (about 30–80 cm^3) the 30-day mortality rate is about 30% due to hematoma or secondary complications; about one third of the patients will be dependent on an outside help for daily living and a third will be capable of independent existence. Age >60 years, Glasgow Coma Score ≤6 at the time of admission, intracranial hemorrhage volume >30 ml, midline shift in CT scan >3 mm and presence of intraventricular hemorrhage and hydrocephalus will all have an adverse impact on outcome. Young age, Glasgow Coma Score >8, intracranial hemorrhage volume <20 ml and absence of intraventricular hemorrhage/hydrocephalus are associated with more favorable outcomes [10].

Widespread use of neuroimaging in mildly symptomatic patients has led to the discovery of *small or minor putaminal hemorrhages*. In such cases, the volume of hematoma is modest (1–20 cm^3), the internal capsule involvement is occasional and partial, intraventricular hemorrhage or ventricular compression are absent. The clinical features of these small hemorrhages are largely similar to the classical lacunar syndromes: the patient is awake, without pupillary abnormalities or deficits in eye movements, the signs of intracranial hypertension (headache, vomit) are rarely present, but pure motor hemiparesis, pure sensory stroke, sensorimotor stroke, ataxic hemiparesis, and clumsy-hand dysarthria may occur from time to time [8]. If a *pure motor hemiparesis* occurs, the patient has a paralysis of face, arm and leg on one side, unaccompanied by sensory signs, visual field defect, dysphasia or apractagnosia. In autopsy studies, pure motor hemiparesis has been reported in patients with involvement of the corona radiate or internal capsule (especially the genu and posterior limb). *Pure sensory stroke* is less common than pure motor hemiparesis: the symptoms are restricted to a persistent or transient numbness and mild sensory loss on one side of the body, including the face, arm and leg, without associated hemiparesis, visual field defect, brainstem dysfunction, memory loss, dyslexia, or other deficits [11]. In most of these cases a small hemorrhage encompasses the corona radiata and the posterior limb of the internal capsule [12]. A few pathologically confirmed cases have been described of *sensorimotor stroke* following putaminal hematoma. In these patients

a motor and a sensory deficit coexist. *Ataxic hemiparesis* has also been described in several hemorrhagic lesions and consists of ipsilateral ataxia and crural paresis, in a sort of combination of weakness and incoordination, on the same side of the body. Fisher and Cole [13] described ataxic hemiparesis as 'weakness of the lower limb, especially the ankle and toes, and a Babinski sign, associated with striking dysmetria of the arm and leg on the same side'. The pathologic origin of these symptoms is the simultaneous interruption of the pyramidal systems and the frontopontocerebellar systems, as when if the hematoma involves the corona radiata and the anterior limb of the internal capsule at the same time [14]. A putaminal hemorrhage may also produce *dysarthria-clumsy hand syndrome*, characterized by the combination of facial weakness, dysarthria and dysphagia, with mild hand weakness and clumsiness [15]. Here there is difficulty pronouncing or forming words due to inadequate movements of the muscles of the larynx, the tongue and other muscles in the mouth; with complaining of clumsiness of hand movements on one side of the body. Dysarthria-clumsy hand syndrome may be described as a variant of ataxic hemiparesis, due to lesions involving the internal capsule and the junction between the capsule and corona radiata. In few cases, patients with putaminal hemorrhages may present movement disorders, including *hemichorea-hemiballism and dystonia* when hematoma involves the contralateral subthalamic and putaminal-pallidal regions or the posterolateral thalamus [16]. In all the above-mentioned patients suffering from a small or minor putaminal hemorrhage, neurological deficits are usually stable and the recovery rate is high, with no significant or only slight residual disability.

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Lobar Hemorrhages

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Abstract

The lobar localization of a spontaneous intracerebral hemorrhage occurs in one third of all cases; the most frequent cause is represented by amyloid angiopathy. The clinical symptomatology depends on the dimensions of the hematic collection and of the lobe. The diagnosis is made by CT, but also MRI must performed in order to exclude any vascular malformation or neoplasms, and in young patients a cerebral angiography must be done in order to exclude small arteriovenous or dural malformations.

Primary intracerebral hemorrhages are caused by spontaneous bleeding, i.e. not provoked by neoplasms, aneurysms, vascular malformations or traumas; their incidence is around 12–15 cases per 100,000 persons [1]. These spontaneous intracerebral hemorrhages are localized on the nucleus of the basis, the internal capsule, the brain and the brainstem, but in one third of the cases the hematomas are localized in the cortical and subcortical part: in this case, the intracerebral hemorrhage is defined as 'lobar' [2]. Even if during recent decades several important results have been achieved in the treatment of ischemic and hemorrhagic ictus provoked by vascular malformations, the improvements have been less significant in the treatment of intraparenchymatous hemorrhage and the prognosis of the patients is still insufficient. The social impact of the hemorrhagic ictus is amplified by the fact that usually the patients with this disease are around one decade younger than those affected by ischemic ictus.

Physiopathology

There is always more than one cause of intracerebral hemorrhage and usually there are several factors which are responsible for the bleeding, even though each of them can have a different influence. These factors can be divided into three categories: (a) structural factors (lesions or vascular malformations), (b) hematic-dynamic factors, referable to the arterial pressure, and (c) hemostatic factors, referable to the platelets' functionality and to the coagulation system: the lobar hemorrhages are attributed to the amyloid angiopathy, which is an affection caused by the deposits of amyloid protein in the cortical arterioles [3–6].

The hemorrhages associated with the amyloid angiopathy form in the area that divides the cerebral cortex from the white matter, and can develop toward the encephalic surface, filling the subarachnoid spaces [7]. Some factors such as cranial traumas of a thrombolytic therapy can sometimes facilitate the rupture. There are no advanced signals that can foresee an intracerebral hematoma, even if there are non-hemorrhagic

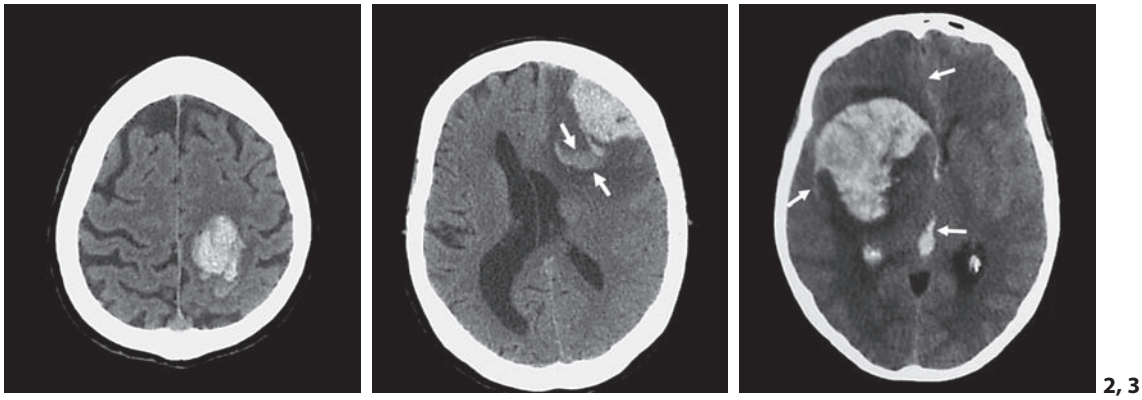

Fig. 1. CT without contrast medium shows a left rolandic circumscribed hemorrhage. The patient has a sudden palsy of the right inferior limb, without sensory alteration.
Fig. 2. CT without contrast medium shows a large left frontal hemorrhage with hernia under the cerebral falx and fluid level (arrows). The patient was subjected to warfarin therapy.
Fig. 3. CT without contrast medium shows a right frontal-temporal hemorrhage with blood traces in the sylvian cistern, in the subarachnoid spaces, and in the interhemispheric area (arrows). Cerebral angiography showed an aneurysm of the medium cerebral artery.

appearances such as an intellectual decline, associated with an arteriosclerotic alteration of the white matter (leukoaraiosis) that must not be undervalued [8].

Intracerebral hemorrhage is not a monobasic event that stops suddenly: the hematoma continues to expand for 6 h in patients without disturbing the coagulation, and up to 24 h in patients affected by coagulopathies [2, 9]. The edema around the hemorrhage reaches its peak after 72 h and remains for several days, even up to 2 weeks [10]. The perilesional edema causes the secondary neuronal damage: the vasogenic and cytotoxic edema determine a destruction in the hematoencephalic barrier and of the sodium pump, with consequent cellular death.

Clinical Onset and Radiologic Diagnosis

The clinical presence of a lobar hemorrhage depends on the dimension of the bleeding. In the large hemorrhages the beginning is sudden, with a rapid decline of the sensory functions and an appearance of neurological deficits caused by the endocranial hypertension: clinically it could be difficult to distinguish a cerebral hemorrhage from an ischemic ictus. If, on the contrary, the hemorrhage has reduced dimensions (fig. 1), the conscience level can be altered and neurologic deficits can appear that depend on the affected lobe, such as hemiparesis, hemianesthesia, lateral hemianopsia, and aphasia. Of the patients who were awake at the beginning, 25% showed a decline of sensory functions in the following 24 h.

The patient affected by a suspect intracerebral hematoma must be immediately subjected to a cerebral computerized tomography (CT): the blood appears hyperdense with the CT without contrast, done soon after the ictus, though a fluid level in the case of a coagulopathy or anticoagulation could be noticed (fig. 2). The localization of the hemorrhage associated with the symptomatology and the presence of other risk factors helps to determine the possible cause of the bleeding, and it can determine the necessity

to undertake further studies. A temporal or frontal lobar hemorrhage associated with the presence of blood in the sylvian cistern or in the interhemispheric space is an indication of a broken aneurysm (fig. 3), while the presence of big vessels inside or outside the hematic collection are related to the presence of a tumor or a cavernous angioma.

The volume of the hematoma can be rapidly calculated with cerebral CT. It represents an important prognostic indicator, since the bigger the shape, the worse the prognosis is [11]. The volume is calculated in cubic centimeters using the formula [12]: $(A \times B \times C)/2$, where AS is the maximum diameter of the hematoma, B is the perpendicular diameter in relation to A with the same slice, and C is the tightness of the hematoma calculated as the number of axial cuts on CT multiplied by the slice thickness in centimeters. In the lobar hemorrhages MRI is always done so as to exclude the presence of vascular malformations or bleeding tumors. If the first MRI is negative, the examination must be repeated 4–6 weeks later when the hematoma has been reabsorbed, since the blood could hide pathologic vessels or neoplasms [13]. Cerebral angiography with digital subtraction must always be done in young patients without risk factors in order to exclude small arteriovenous malformations (cerebral or dural) or arteriopathies [14].

Lobar Hemorrhage and Endocranial Hypertension

The cranium can be compared to a box, inside which there are three components that are equilibrated with each other and keep the pressure constant: the cerebral substance, the blood inside the vessels, and the cerebrospinal fluid that is inside the ventricular cavities and in the subarachnoid spaces. The increase of the volume of one of these elements determines an increase of the endocranial pressure (PIC). In the case of cerebral neoplasms the increase of volume is slow and balanced by the diminution of one of the other elements volume (Monroe-Kellie study), but, in the occurrence of an intraparenchymal hemorrhage, the hematic collection's volume increase will be so instantaneous that the balancing processes could fail with a consequent endocranial hypertension.

Since the cerebral perfusion pressure (PPC) is determined by the difference between the medium arterial pressure (PAM) and PIC, it follows that every therapeutic care must keep the PIC constant in order not to diminish the PPC below 70 mm Hg [11]. The patients with a Glasgow Coma Score below 8 should be subjected to a monitoring of PIC with an intraparenchymal catheter; it would be even better to use an intraventricular one because the liquoral subtraction can help diminish the PIC. Other therapies to diminish the PIC include the use of diuretic medicines (mannitol or hypertonic solutions), automatic hyperventilation, neuromuscular arrest [15], and surgical removal of clots.

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Subarachnoid and Intraventricular Hemorrhage

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Abstract

Subarachnoid hemorrhage (SAH) accounts for 5% of all strokes but its burden is relevant due to high mortality, high disability and a remarkable incidence in the young. The rupture of an intracranial aneurysm is responsible for about 85% of SAHs; 10% are represented by non-aneurysmal conditions; 5% are represented by other medical conditions such as inflammatory or non-inflammatory lesions of cerebral artery, coagulopathy, neoplasms or drug abuse. The clinical presentation of a SAH can be extremely variable ranging from nearly asymptomaticity to sudden death. Rebleeding is the most frequent and severe complication of SAH. The aneurysm exclusion is the most effective treatment for preventing rebleeding. Endovascular occlusion of the aneurysm with coils has been shown to be associated with better short- and long-term outcomes than surgical clipping in select patients.

Subarachnoid hemorrhage (SAH) is a neurologic emergency due to blood extravasation in the space delimitated from pia mater to arachnoid (fig. 1). Even if it accounts for 5% of all strokes the burden of SAH is relevant due to high mortality, high disability and a remarkable incidence in the young.

Epidemiology and Pathophysiology

The incidence of SAH is about 6–7 cases out of 100,000 per year; it tends to increase with age but half of the patients are younger than 55; it prevails in the female gender with a ratio of 1.6 compared to males. The mortality rate is about 50%; most deaths occur within 2 weeks; 10% of patients die before reaching the hospital [1–4].

The rupture of an intracranial aneurysm is responsible for about 85% of SAHs; 10% are represented by non-aneurysmal conditions; 5% are represented by other medical conditions such as inflammatory or non-inflammatory lesions of cerebral artery, coagulopathy, neoplasms or drug abuse (table 1); focal SAH can be associated with cerebral amyloid angiopathy.

Cerebral aneurysms are present in 2–3% of the population. They are mostly located at the bifurcation of Willis polygon vessels or their branches (fig. 1). The risk of rupture is quite low, estimated at about 0.05% per year, but it can increase when the diameter is >10 mm or if located at the cerebral posterior circulation. An international study has reported that the cumulative risk of rupture at 5 years is zero for aneurysms <7 mm, 2.6% for dimensions between 7 and 12 mm, 14.5% for dimensions between 13

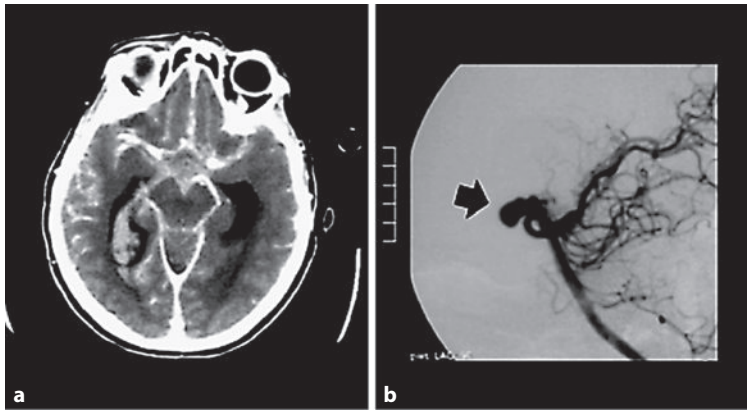

Fig. 1. **a** Massive SAH with ventricular invasion. **b** Saccular aneurysm of the basilar artery.

Table 1. Causes of SAH

Aneurysmal SAH
Non-aneurysmal perimesencephalic SAH
Other medical conditions:
Inflammatory lesions of cerebral arteries
Mycotic aneurysms
Borreliosis
Behçet's disease
Primary angiitis
Polyarteritis nodosa
Churg-Strauss syndrome
Wegener's granulomatosis
Non-inflammatory lesions of intracerebral vessels
Arterial dissection
Cerebral arteriovenous malformations
Cerebral dural arteriovenous fistulae
Cerebral venous thrombosis
Vascular lesions in the spinal cord
Saccular aneurysm of spinal artery
Spinal arteriovenous fistula or malformation
Cavernous angioma at spinal level
Coagulopathies
Tumors
Drugs
Anticoagulant drugs
Cocaine

and 24 mm, and 40% for aneurysms >25 mm. Those rates increase respectively at 2.5, 14.5, 18.4 and 50% for aneurysms located at the posterior circulation.

Modifiable risk factors for aneurysm rupture include arterial hypertension, smoking, alcohol abuse and cocaine use. Genetic factors are determinants as demonstrated by the increased risk in first-degree relatives. Connective hereditary diseases such as polycystic kidney, Ehlers-Danlos (type IV) syndrome, pseudoxanthoma elasticum and fibromuscular dysplasia are conditions associated with intracranial aneurysms and SAH.

Perimesencephalic non-aneurysmal SAH is characterized by blood extravasation into the cisterns around the midbrain, pons or at the level of the quadrigeminal cistern, without reaching the sylvian fissure or interhemispheric fissure or ventricular system. Perimesencephalic SAH is usually not due to aneurysmal malformation and is associated with a good outcome. The normality of angiographic findings supports the venous origin of the bleeding due to the rupture of a prepontine or interpeduncular vein. In these patients the perimesencephalic veins frequently drain directly into the dural sinuses instead of into the vein of Galen, predisposing to venous congestion.

Clinical Features

The clinical presentation of a SAH can be extremely variable ranging from nearly asymptomaticity to sudden death. This is believed to be responsible for a 12% of misdiagnosis with potentially severe consequences in the late treated cases.

Headache is the most common symptom and is the only symptom in one third of patients. It is mainly located in the occipital-nuchal region and is of severe intensity, described often as the most intense ever experienced, typically with sudden onset. The rapidity in reaching the maximum intensity, within a few seconds, is more indicative than the intensity itself. Nausea, vomiting and photophobia can be present but they are not specific as they are frequently associated with primary headaches or other secondary headaches. 75% of patients with thunderclap headache have a SAH.

Two thirds of patients on admission present a decreased level of consciousness; half of them are in coma. Confusion and agitation can be present. Nuchal rigidity is a clinical sign of meningeal irritation due to the blood extravasation in the subarachnoidal space. Other signs of meningeal irritation include a positive Lasegue sign or Kernig and Brudziski signs. Meningeal signs can take from 3 to 12 h to develop and can be completely absent in the case of coma or minimal blood extravasation. Thus, the absence of neck stiffness cannot exclude the diagnosis of SAH.

Seizures can be present in 7% of all patients. Young age (<40 years), entity of the bleeding, presence of hydrocephalus and early rebleeding are the main risk factors for early seizures while vasospasms with cortical ischemia, intraparenchymal bleeding and neurosurgery instead of endovascular treatment are risk factors for late-onset seizures. About 14% of patients can present intraocular hemorrhage: the sudden increase in intracranial pressure can lead to a central retinal vein occlusion with subsequent preretinal (subhyaloidal) blood extravasation. In the case of severe bleeding, hemovitreous can occur (Terson syndrome). Focal neurological deficits are not typical findings in the acute phase of subaracnhoid hemorrhage, but they may occur in case of intraparenchymal extension of bleeding, compression of cranial nerves or ischemic lesions due to early vasospasm. Cardiovascular changes, mainly hypertension and tachycardia due to the adrenergic tone, can be present in the acute phase; a sudden cardiac arrest can occur at the onset in 3% of cases.

Diagnostic Studies

Brain computed tomography (CT) scan is the first level instrumental investigation if a SAH is suspected. This examination can show the hyperdensity of the extravasated blood in the subarachnoidal space with a sensitivity depending on the amount of bleeding and the interval after symptom onset. The CT scan will be positive in 97% of the cases if carried out within 12 h; this percentage decreases to 93% at 24 h and is 50% 1 week after symptom onset. Moreover, a CT scan can evidence intraparenchymal or intraventricular extension of bleeding, hydrocephalus, cerebral edema or ischemic lesions due to vasospasm.

Magnetic resonance imaging (MRI) with proton density, FLAIR and gradient echo images is as sensitive as CT in the acute phase whilst it becomes more sensitive than CT after the initial days. MRI can permit a preliminary cerebral blood vessel evaluation without contrast medium with magnetic resonance angiography whereas with diffusion images it allows for the detection of ischemic lesions. In contrast, MRI takes longer to acquire images and needs patient collaboration; this limits a widespread application in the acute phase.

In case of a clinical suspect of SAH and negative neuroimaging, cerebrospinal fluid (CSF) examination is required. The most informative CSF test is obtained 6–12 h after symptom onset and should be focused on the presence of bilirubin, hemoglobin catabolite, that provides CSF with the characteristicxanthochromia.Spectrophotometry can allow for a more sensitive determination.

Following the diagnosis of SAH, determining cause and localization of bleeding is mandatory. The pattern of blood extravasation can suggest the site of aneurysm rupture, particularly for aneurysms of the anterior communicating artery, which have bleeding in the interhemispheric fissure or aneurysms of the middle cerebral artery, which have bleeding in the sylvian fissure; while posterior circulation aneurysms have no common pattern. Isolated extravasated blood on the anterior part of the brainstem permits the diagnosis of perimesencephalic SAH with a more favorable outcome even if in the 5% of cases a vertebrobasilar aneurysm can be present.

CT angiography has a 95% sensitivity to detect ruptured aneurysms. Magnetic resonance angiography reproduces the same results but, as it requires patient collaboration, it is not suitable for critical patients.

Digital catheter angiography is the gold standard. Furthermore, it can give information about the morphological features of the aneurysms and its relations with other arteries thereby permitting better treatment planning. The angiographic study must be extended to all the cerebral arteries as in the 15% of cases multiple intracranial aneurysms can be present. In 1–2% of cases angiography can be complicated by aneurysm rupture and in 1.8% of cases by neurological complication with possible permanent sequelae.

Clinical Complications

Rebleeding is the most frequent and severe complication of SAH. It can occur in the first 24 h in about 15% of patients with a cumulative risk of 40% in the first month and an incidence of 3% per year after 6 months. Rebleeding is associated with a poor outcome: mortality and disability can reach 80%.

Cerebral ischemic lesions can occur in the acute phase as a consequence of the sudden increase in intracranial pressure with the secondary decrease in cerebral perfusion pressure. More frequently, ischemic complications develop later, with a peak between 4 and 14 days from symptom onset, due to vasospasm. Usually, the focal neurological deficits show a less acute onset with respect to atherothrombotic or cardioembolic ischemic stroke and frequently more arterial territories are involved.

The presence of blood in the ventricular system can cause alterations in CSF circulation leading to an acute hydrocephalus. The clinical presentation is usually represented by a progressive decrease in consciousness with possible associated focal neurological deficits. Cardiovascular complications are represented by drug-resistant hyper- or hypotension, arrhythmias or heart failure. Other possible complications are hydroelectrolyte disorders with hypo- or hypernatremia and hypomagnesemia; hyperglycemia and fever can occur.

Treatment

SAH is a clinical emergency with high mortality from onset. First of all, the stability of respiratory and cardiovascular functions needs to be evaluated and treated if required. After the vital functions are stabilized the second step is to prevent rebleeding and other possible complications that can compromise patient prognosis. Hypertension must be treated promptly with endovenous antihypertensive drugs such as labetalol or urapidil if needed. Recommended systolic blood pressure values are between 140 and 90 mm Hg; after the exclusion of the aneurysm the blood pressure treatment can be less intensive. Considering the risk of hypoperfusion, hypotension should be avoided even if definite target values are not established.

Nimodipine 60 mg orally every 4 h for 21 days can reduce the risk of delayed cerebral ischemia due to vasospasm. A Cochrane revision has reported a relative risk reduction of 18% with an absolute risk reduction of 5.1%. Antifibrinolytic agents can reduce the rate of rebleeding even if they increase the risk of cerebral ischemia or systemic thrombosis. Tranexanic acid reduces the

rebleeding rate from 11 to 2.4%, but this benefit is offset by ischemic complications. The aneurysm exclusion is the most effective treatment for preventing rebleeding. Over the last decades, endovascular coiling has become the first choice treatment with respect to the neurosurgical clipping showing an absolute risk reduction of 7%. Nevertheless, this technique is not suitable for all aneurysms: wide neck and close relations with vessel branches require a neurosurgical approach.

Table 2. Causes of primary IVH

Intraventricular arteriovenous malformation
Intraventricular aneurysm
Intraventricular cavernoma
Choroid plexus malformation
Choroid plexus hemangioma
Fourth ventricle ependymoma
Coagulation disorders
Leukemia and lymphoma
Cocaine abuse
Vasculopathies (Moyamoya disease)

Intraventricular Hemorrhage

Primary intraventricular hemorrhage (IVH) is a rare form of intracranial bleeding accounting for about 3% of all intracranial hemorrhages. The site of bleeding is the vasculature of the subependymal region or the choroid plexus. Causes of primary IVH are listed in table 2. IVH can also occur following rupture of a parenchymal hemorrhage into the ventricular system, especially in caudate, putamen, thalamic or large lobar hemorrhages as well as in generalized SAH (secondary IVH). Clinical presentation depends on the amount of intraventricular blood and its distribution. Symptoms of minor IVH include sudden onset of severe headache, nausea, vomiting and neck stiffness; focal neurological deficits are unusual. In severe IVH there is a decrease consciousness to stupor and coma, focal or generalized seizures and signs of brainstem compression may occur. Communicating hydrocephalus is a common complication. In massive IVH a surgical evacuation is recommended; thrombolytic treatment into the ventricle can favor the resolution of intraventicular clot while ventricular drainage is needed if an hydrocephalus occurs.

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Large Middle Cerebral Artery and Panhemispheric Infarction

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Abstract

Large middle cerebral artery (MCA) and panhemispheric stroke represent a minority of cerebral ischemic events, yet they are responsible for a disproportionate share of morbidity and mortality. Malignant infarction with formation of cerebral edema is a common cause for secondary neurologic deterioration. Despite intensive medical and surgical care, prognosis is often poor and mortality may be as high as 60–80%. Surgical intervention can reduce that mortality compared to medical therapy alone, but necessitates a careful exploration of patient characteristics for acceptable outcomes.

Although space-occupying, large middle cerebral artery (MCA) and panhemispheric infarction have not been identified as a distinct nosographic entity, their definition is widely accepted and usually based on clinical presentation, typical clinical course, and neuroradiological findings. We define these infarcts as those that involve the majority of the territory supplied by the MCA, the territory supplied by the MCA and the anterior cerebral artery (ACA), the territory supplied by the MCA and the posterior cerebral artery (PCA), or all the three territories combined. Infarction in the territory of the anterior choroidal artery may also be included. The resulting increased intracranial pressure and tissue shifts lead to further destruction of formerly healthy brain tissue, giving rise to the so-called 'malignant' infarction [1].

Epidemiology and Risk Factors

Severe hemispheric stroke represents a minority of ischemic strokes accounting for up to 10% of patients with supratentorial ischemia [1, 2]. The yearly incidence of a malignant acute ischemic stroke is between about 10 and 20 per 100,000 persons [1, 3]. Compared with other patients with ischemic stroke, substantially fewer of those who have malignant MCA infarction have a history of ischemic stroke. Moreover, women, younger subjects, and those with involvement of the anterior choroidal artery are more likely to be affected [3, 4]. The etiology of hemispheric infarctions is mostly due to thrombosis or embolic occlusion of either the internal carotid artery or the proximal MCA. Anatomical variances and pathological findings that predispose an individual to a hemispheric infarction include abnormalities of parts of the ipsilateral circle of Willis (mainly a hypoplasia or an atresia) and an insufficient number

and caliber of leptomeningeal collateral vessels that are available for collateralization [4].

Clinical Features

Some of the early clinicopathological correlations were made by Foix and Lévi [5] at the beginning of the 20th century. They described the *varieté massive de l'hémiplégie* due to total infarction of the MCA territory seen at autopsy, and their description contained many of the elements that we are familiar with today. Uncollateralized occlusion of the main trunk of the MCA causes softening of the basal ganglia and internal capsule, and a large portion of the cerebral surface and subcortical white matter. Contralateral hemiplegia and hemianesthesia are characteristic findings of severe hemispheric infarcts. Involvement of the contralateral leg is common, due to the interruption of the descending white matter fibers in the internal capsule, even when the cortical gray matter subserving this functional region is spared. Hemianopia develops from interruption of the optic radiations. The frontal eye fields frequently define the anterior extent of the typical severe infarction, and cause gaze deviation to the side of the infarct. In dominant hemispheric stroke, there is global aphasia. The posterior extent of the infarct is often demonstrated by the presence of neglect, but can be difficult to assess in the setting of aphasia. Alternatively, diminished optokinetic nystagmus can identify involvement in the parieto-occipital gaze centers, and does not require the ability to follow commands to perform the test. In non-dominant hemispheric stroke, dense neglect and apraxia reliably define the posterior extent.

Loss of Consciousness

Transient loss of consciousness as the initial sign occurs rarely in cases of hemispheric infarction. Delayed loss of consciousness between 36 h and 4–5 days is more common as the consequence of cerebral herniation and does not result from an involvement of a specific brain region. Clinically we can recognize two different syndromes associated with supratentorial lesions: central downward transtentorial herniation (displacement of the diencephalon caudally through the tentorial incisura) and herniation of the temporal lobe (uncal herniation syndrome; displacement of the temporal lobe uncus medially over the edge of the tentorial incisura).

Anatomopathological studies indicate that the swelling reaches a maximum within 2–5 days and then gradually resolves. Cerebral edema causes worsening of signs and a decline in the level of consciousness in about one-fifth of cases of acute massive supratentorial infarction and one-half of patients who present rostral-caudal deterioration after ischemic stroke go on to die. The NIHSS score captures many of these clinical features, and dominant severe hemispheric infarctions tend to exhibit scores ≥20 and non-dominant infarctions ≥15. Additional clinical and radiographic features are associated with early cerebral edema and poor neurologic outcomes (table 1). Secondary neurologic deterioration typically ensues within 2–5

Table 1. Clinical and radiographic predictors of poor outcome or death in severe hemispheric stroke

Clinical
Nausea, vomiting
Reduced arousal
NIHSS >20 (dominant hemisphere)
NIHSS >15 (non-dominant hemisphere)
Elevated SBP >10 mm Hg
Congestive heart failure
Radiographic
Hyperdensity >50% MCA territory on CT scan <6 h
Swelling visible on initial CT scan
Multiple vascular territories involved (ACA or PCA and MCA)
Incomplete circle of Willis
Midline shift >5 mm

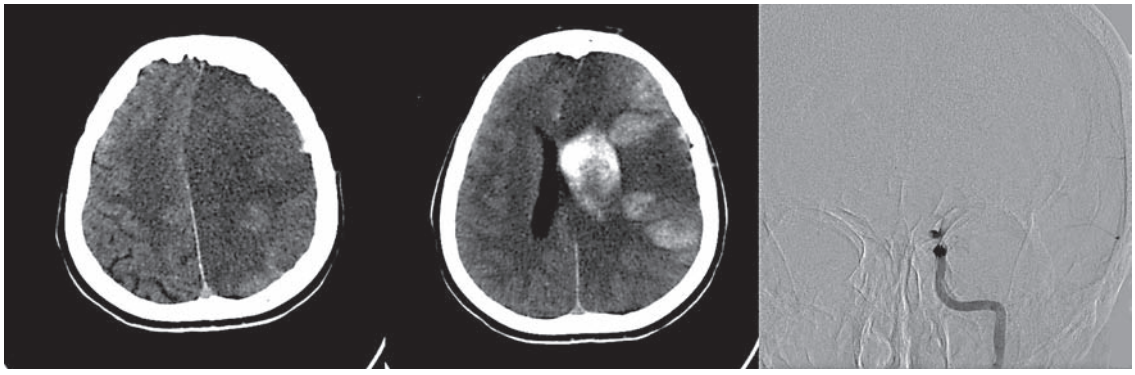

Fig. 1. Large panhemispheric infarct with hemorrhagic transformation due to occlusion of the internal carotid artery in a 56-year-old woman (kindly provided by Prof. R. Gasparotti, Neuroradiology, University of Brescia).

days after presentation. Key clinical findings include young age, a high initial NIHSS score, an elevated systolic blood pressure ≥180 mm Hg at 12 h, the development of nausea and vomiting within the first 24 h, and a progressive decline in the level of arousal over the first couple of days. Late findings include unilateral or bilateral pupillary dilatation. A radiographic feature that predicts malignant cerebral edema and poor prognosis includes hypodensity on head CT within the first 6 h and ≥50% of the MCA territory. The involvement of multiple vascular territories (i.e. MCA and either ACA or PCA), or midline shift >5 mm within the first 2 days, are also associated with early mortality [6]. Because no single factor can predict who will develop secondary neurologic deterioration in severe hemispheric stroke, intensive neuromonitoring is indicated until the peak period of cerebral edema has passed after day 5 or 6. Generally, a neuroradiological definition of malignant MCA infarction assumes that at least two-thirds of the MCA territory is affected. Other authors predict a malignant course with development of severe edema if more than 50% of the rostral MCA territory and the basal ganglia show ischemic alterations. Additionally, infarctions of the ipsilateral ACA or PCA can occur concomitantly with MCA infarctions (fig. 1).

Approach to Severe Hemispheric Stroke

An immediate intensive care in a specialized neurocritical care unit is required for patients with large, space-occupying cerebral infarctions. Sedation, intubation, and mechanical ventilation in order to prevent aspiration and to allow invasive treatment to be started are often indicated early, and even electively once the malignant course of the disease has been verified [7].

Pharmacological Approaches

There are many pharmacological approaches to the prevention and management of the developing brain edema. Treatment with osmotic compounds, such as mannitol, glycerol, and hypertonic saline, reduces increased intracranial pressure and seems to affect outcome, but their efficacy has not yet been proven in randomized clinical trials. All other approaches, such as barbiturates, hyperventilation, head elevation, Tris-hydroxymethyl-aminomethane (THAM) buffers, indomethacin, steroids, furosemide, are not supported by adequate evidence of efficacy from clinical trials.

Hypothermia

Moderate hypothermia with target temperatures between 33 and 35°C, achieved with endovascular catheters, is a promising approach for

neuroprotection in patients with large MCA infarctions [8]. Results from various animal studies have been confirmed by data from clinical observational studies (although only a few patients treated with moderate hypothermia were analyzed), which indicate both a reduced mortality and a good functional outcome in the surviving patients. However, the findings should be considered as preliminary because there is no evidence from randomized trials on the efficacy of cooling as a treatment for hemispheric infarction.

Surgical Approach

Recently, several randomized trials (DECIMAL trial, DESTINY trial and HAMLET trial) demonstrated that early hemicraniectomy in patients <60 years reduces mortality from about 70 to 20% without increasing the risk of being very severely disabled. Hemicraniectomy increases the chance to survive completely independent more than fivefold and doubles the chance to survive at least partly independent. In patients >60 years (about 50% of malignant MCA strokes) mortality and poor outcome were significantly higher than in younger patients but still less than in patients who did not receive surgery (DESTINY II trial) [9]. Although several issues remain to be addressed (patients' age limit and timing of surgery among the others) decompressive surgery is a promising treatment option for these patients.

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Midbrain Infarcts and Hemorrhages

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Abstract

The vascular supply of this small brainstem structure is complex. Although midbrain infarcts and particularly hemorrhages are uncommon, their clinical manifestations are diverse mainly because the vertical gaze centers and two of three nuclei of the extraocular muscles lie primarily in the midbrain. Consequently, eye movement disturbances are often the hallmark clinical findings in midbrain stroke. The main clinical patterns, etiology and outcome of infarcts limited to the midbrain are summarized according to defined vascular territories along with the clinical findings of midbrain hemorrhage.

Midbrain Infarcts

Midbrain infarcts account for 2% of all cerebral infarcts, whereas their frequency increases up to 8% in infarcts limited to the posterior circulation [1–3]. Isolated midbrain infarcts are infrequent because of the midbrain's common vascular supply with other infra- or supratentorial anatomical sites. Midbrain infarcts more often coexist with infarcts in neighboring structures (diencephalon and pons) or the temporo-occipital cortex and superior cerebellum [1, 2]. The midbrain's vascular supply is quite elaborate and depends on midbrain level, where the contribution of the posterior cerebral artery increases caudorostrally. Four vascular territories are relatively constant, the most often involved being the anteromedial (paramedian) and anterolateral territories at the middle and upper midbrain [1–3].

Anteromedial (Paramedian) Territory

Penetrating perforators from the basilar artery supply the anteromedial midbrain. Critical structures for vertical gaze (posterior commissure, periaqueductal region and the rostral interstitial nucleus of the medial longitudinal fasciculus) reside at the upper midbrain tegmentum; thus, infarcts involving the territories of the paramedian perforators of the basilar artery, perforating branches of the superior cerebellar artery or the posterior thalamo-subthalamic paramedian artery (branch of the P1 segment of the posterior cerebral artery) can produce vertical gaze palsies.

A diversity of conjugate or disconjugate supranuclear vertical gaze palsies (rarely in isolation), can be prominent findings of upper midbrain ischemia resulting from bilateral and, less commonly, unilateral upper midbrain infarcts (table 1) [1–4]. Uni- or bilateral paramedian thalamic infarcts also cause vertical gaze abnormalities together with decreased level of consciousness and neuropsychological disturbances, whereas complete bilateral ophthalmoplegia (bilateral ptosis with loss of all extraocular movements) is an unusual sign of bilateral infarcts at the mesodiencephalic junction.

Table 1. Eye movement disorders associated with midbrain infarcts

Paramedian rostral midbrain infarcts
Supranuclear conjugate gaze palsies
Combined up and down gaze palsies; selective up or down gaze palsy
Complete ophthalmoplegia (bilateral ptosis with loss of all extraocular movements)
Dorsal midbrain syndrome (Parinaud's syndrome)
Convergence-retraction and see-saw nystagmus
Pseudoabducens palsy
Peering at the tip of the nose (tonic inward and downward deviation of the eyes)
Supranuclear disconjugate gaze palsy:
Monocular elevation palsy (double elevator palsy)
Prenuclear syndrome of the oculomotor nucleus
Vertical one-and-a half-vertical syndrome
Skew deviation
Paramedian middle midbrain infarcts
Nuclear third nerve palsy: ipsilateral third nerve palsy, bilateral mydriasis and contralateral superior rectus palsy (most common pattern
Paramedian caudal midbrain infarcts
Isolated INO or associated with fourth nerve palsy, bilateral ataxia, and dissociated vertical nystagmus
Anterolateral middle midbrain infarcts
Fascicular third nerve palsy: isolated (inferior rectus palsy, superior rectus palsy, medial rectus palsy, third nerve palsy with pupil sparing, bilateral ptosis) or associated with crossed hemiplegia, ipsilateral or contralateral hemiataxia, and abnormal movements

Midbrain paramedian rostral infarcts can also manifest without neuro-ophthalmologic signs; thus, pure motor hemiparesis or isolated gait ataxia have been observed when ischemia exclusively affects the midbrain's ventral portion. When ischemia is located around the red nucleus, the predominant feature may be body lateropulsion (contraversive falls to the side of lesion) due to interruption of ascending fibers of the crossed dentatorubrothalamic pathway.

Nuclear third nerve palsy (isolated or associated with hemiparesis or ataxia) is a localizing sign of paramedian territory infarct at the middle level of the midbrain [1, 3, 4]. The most common pattern of nuclear oculomotor disorder is ipsilateral third nerve palsy with contralateral superior rectus paresis, often with bilateral ptosis and mydriasis [1]. Dysarthria, often associated with other signs, can be found in half of patients with pure midbrain infarction, whereas dysarthria (hypokinetic and palilalia) as the prominent clinical manifestation can be due to a single ischemic lesion involving the medial ventral part of the substantia nigra. Acquired stuttering can, in rare instances, be the outstanding manifestation of a small midbrain ischemia.

At the lower paramedian midbrain level, tetraataxia – often associated with hemiparesis, delayed tremor or palatal myoclonus – is a rare occurrence following bilateral or, less commonly, unilateral infarcts involving the crossing efferent dentatorubral fibers [1]. Uni- or bilateral internuclear ophthalmoplegia (INO) due to involvement of the

medial longitudinal fasciculus together with limb or gait ataxia, dysarthria and tremor, can reveal a caudal paramedian infarct, whereas isolated bilateral INO is less common. Pathological laughter, although very rare, can herald a paramedian lower midbrain infarct (associated with dysarthria and hemiparesis) that disrupts the brainstem-basal ganglia-forebrain circuitry participating in laughter control.

Anterolateral Territory

This territory is served by mesencephalic arteries stemming from the P2 segment of the posterior cerebral artery. A peripheral type of oculomotor nerve palsy (often characterized by unilateral adduction and upward and downward palsy with ptosis and mydriasis), sometimes without other major signs, is the most prominent sign of infarct at the middle midbrain level [1, 4]. Hemiataxia, hemiparesis and abnormal movements can also be found (although not as frequently as supposed) in association with fascicular third nerve palsy, corresponding to the classic eponymous midbrain syndromes of Claude's, Weber's and Benedikt's, respectively. Ataxic hemiparesis or hypesthetic ataxic hemiparesis have also been described. Acute onset hemiparkinsonism or parkinsonism predominantly affecting the lower limbs, along with mild or no resting tremor, is a very rare occurrence in a single strategic infarct at the level of the substantia nigra pars compacta, whereas uni- or bilateral ischemias involving the substantia nigra pars reticulata have been associated with peduncular hallucinosis.

Lateral Territory

Short circumferential branches of the superior cerebellar artery feed the caudal two-thirds of the laterodorsal region, and penetrating branches from the choroidal posterior artery supply the upper lateral level. Restricted acral sensory deficits (cheiro-oral and cheiro-oral-pedal), either associated or not with hemiataxia and hemiparesis, are due to damage of the medial and trigeminal lemniscus and are the main clinical findings of lateral infarcts at the middle or caudal level of the mesencephalon [1, 3].

Dorsal Territory

Infarcts exclusively involving this territory are exceedingly uncommon, due to concomitant involvement of the superior cerebellar artery (cerebellar territory). Isolated hemihypesthesia, isolated trochlear nerve palsy, ipsilateral Horner's syndrome and contralateral ataxia have been reported.

Other Patterns of Infarcts

Bilateral infarcts are uncommon, occurring mainly when both paramedian territories at the upper level are affected. In such cases, ischemia may extend to the neighboring thalamus. Different patterns of vertical gaze palsy are the main clinical findings. Locked-in syndrome has been found with restricted ischemia affecting both cerebral peduncles. Oculomotor signs predominate along with hemiparesis and hemiataxia when combined anteromedial and anterolateral infarcts occur [3].

Etiology of Midbrain Infarcts

In four clinical series of midbrain infarcts (two of which also included other posterior circulation infarcts), a total of 74 patients had pure mesencephalic infarcts [1–3]. In these patients, large artery disease (basilar artery stenosis or occlusion) was the leading etiology (42%), small artery disease and cardioembolism were the presumed etiology in 30 and 11% of infarcts, respectively, while in 15% the etiology could not be determined. When midbrain ischemia extends upward and involves the thalamus, superior cerebellum and temporo-occipital cortex, the predominating mechanisms are artery-to-artery or cardiac embolisms [2].

Outcome in Midbrain Infarcts

Most patients with isolated midbrain infarcts have a favorable prognosis: 55–90% of patients remained functionally independent after a follow-up of between 8 and 25 months. Death is a rare occurrence in these cases [2, 3].

Midbrain Hemorrhages

Isolated spontaneous midbrain hemorrhages are uncommon; the midbrain tegmentum is more often involved. Most clinical findings in midbrain infarcts have also been found in mesencephalic hemorrhages, oculomotor disorders being by far the most frequent [5, 6]. Thus, reports include third and fourth nerve palsies, dorsal midbrain syndrome, convergence retraction nystagmus, vertical one-and-a-half syndrome, uni- and bilateral INO, bilateral total ophthalmoplegia and upward and downward gaze palsy. Moreover, pure sensory stroke, scanning dysarthria, Weber's, Claude's and Nothnagel's syndromes, movement disorders (hemiparkinsonism, unilateral asterixis and upper limb dystonia), cognitive manifestations (peduncular hallucinosis and retrograde amnesia) and alteration of consciousness (spindle coma) have also been found, for the most part with small midbrain hemorrhages.

The leading causes of midbrain hemorrhages are vascular malformations (40%) and bleeding diathesis (5%). Arterial hypertension is a less frequent etiology (25%) in the midbrain compared to other brainstem structures. The etiology of midbrain hemorrhages remains undetermined in around one-third of patients [5, 6]. Due to increased recognition of minute midbrain hemorrhages, current prognoses are generally favorable.

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Pontine Infarcts and Hemorrhages

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Abstract

Pontine infarcts are often part of a large ischemia involving the brainstem, although infarcts may be restricted to the pons. In both cases, infarcts in the pons are characterized by interesting clinical patterns resulting from a variety of cranial nerve dysfunctions, eye movement disorders and motor, sensory and cerebellar manifestations, either isolated or in combination. The anteromedial and anterolateral territories are the most commonly involved. Penetrating branch artery disease is the most common etiology. Ten percent of all intracerebral hemorrhages are located in the pons, and small hemorrhages in this brainstem structure may, in some instances, give rise to unusual clinical manifestations.

Pontine Infarcts

The pons, either in isolation or as part of multilevel ischemia, is affected by stroke much more often than other brainstem structures. Infarcts restricted exclusively to the pons account for 12–27% of posterior circulation ischemia [1, 2]. Transient ischemic attacks preceding pontine infarcts may occur in up to one-third of patients and may include unusual manifestations such as pontine warning syndrome, pathological laughter ('fou rire prodromique'), transient excessive yawning, several patterns of transient facial pain (e.g., 'salt and pepper on the face' pain) and clonic arm movements. Based on clinical, anatomical and radiological correlations, the following constant vascular territories have been defined in pontine ischemia: ventromedial (anteromedial), anterolateral, lateral (tegmental), dorsal and bilateral infarcts.

Anteromedial Infarcts

Two out of three isolated pontine infarcts may involve the paramedian territory [1, 2]. The medial basis pontis (corticospinal tract) is supplied by the short midline perforators branching directly off the basilar artery, from which the long midline perforators supply the medial tegmentum (including the medial part of the medial lemniscus, the abducens nucleus, medial longitudinal fasciculus and paramedian pontine reticular formation). Paramedian infarcts often extend to the ventral surface, whereas ischemia restricted to paramedian tegmentum is less common [2, 3]. Moderate to severe pure motor hemiparesis (PMH), more marked in the upper extremity and in the distal part of the limbs, is the main clinical manifestation in approximately one-half of infarcts due to lesions of the ventral surface of the paramedian caudal or middle pons [2]. Distinct lingual, contralateral palatal-lingual or palatal-lingual-laryngeal hemiparesis are uncommon patterns of motor deficit and resemble those observed in capsular genu syndrome. Moderate or marked dysarthria is almost a

constant finding in large paramedian infarcts, particularly of the upper pons, and is often accompanied by hemiparesis, brachial monoparesis, supranuclear facial palsy and hemiataxia, while isolated dysarthria is a rare occurrence [3].

Mild and transitory tegmental dysfunction characterizes most paramedian infarcts and is noticeable by pure lemniscal sensory loss (including cheiro-oral, crural or facial hypesthesia) or associated with motor deficit as well as a broad spectrum of neuro-ophthalmologic signs. The main neuro-ophthalmologic manifestations found in paramedian ischemia, and which almost never occur in isolation, are one-and-a-half syndrome (ipsilateral horizontal gaze palsy to one side and a restriction for adduction to the other), internuclear ophthalmoplegia (INO), ipsilateral horizontal gaze palsy, ocular bobbing, primary-position downbeating nystagmus, skew deviation, Horner's syndrome and abducens nerve palsy [2, 3]. Smaller infarctions in the ventrotegmental junction at the middle upper pons may be associated with dysarthria-clumsy hand syndrome (DCHS) and its variants, and ataxic hemiparesis (AH) and its variants [1, 3]. The most common etiology of anteromedial infarcts is basilar branch disease (occlusion of a penetrating branch from the BA). Functional outcome is favorable; most patients have a mild disability and are independent 9 months after pontine infarct [2, 3].

Anterolateral Territory

This is the second most frequent territory involved in pontine infarcts. It is served by anterolateral pontine arteries supplying the lateral portion of the corticospinal tract and parts of the medial lemniscus. Clinical manifestations of small infarcts include PMH (mild facio-brachio-crural or, less often, brachio-crural hemiparesis) and, less commonly, DCHS and AH and its variants. Tegmental dysfunction is found in nearly 60% of infarcts. The main manifestations are lemniscal sensory loss (brachial or facio-brachio-crural hypesthesia), homolateral conjugate gaze palsy, isolated abducens palsy, one-and-a half syndrome, nystagmus, skew deviation, Horner's syndrome and pursuit movements superimposed with saccades. The causes are basilar artery branch disease and small artery disease in one-half and one-fifth of infarcts, respectively. Functional outcome is favorable in most patients [1, 2].

Lateral Territory

Lateral pontine arteries stemming from the anterior inferior cerebellar artery feed the caudal lateral pons. These arteries, at the upper level, arise from the superior cerebellar artery and supply the pontine nuclei, dorsolateral corticospinal tract, medial lemniscus, ventral trigeminothalamic tract and, more externally, the middle cerebellar peduncle. Frequency of lateral ischemia ranges from 12 to 30% of all pontine infarcts [1, 2].

Motor deficit is not a constant finding in lateral infarcts; when present, a mild facio-brachio-crural hemiparesis, brachio-crural hemiparesis and crural monoparesis (particularly at the upper level) are the main clinical patterns [4]. Contralateral lemniscal or spinothalamic sensory deficits are not always present. Brachio-crural, facio-brachio-crural, arm, trunk and leg or crural hypesthesias have been described; isolated trigeminal weakness with hypesthesia is very uncommon [1, 2]. Neuro-ophthalmologic signs are common and quite similar to those described in other pontine territorial infarcts. These signs are often accompanied by contralateral motor and sensory deficits or ataxia. Tiny laterodorsal infarcts, nevertheless, may manifest as isolated single nerve palsies – VI fascicular or nuclear facial palsy – or painful ipsilateral trigeminal neuropathy. Ischemia at the caudolateral pons is characterized by absence of oculomotor signs; isolated vertigo may be a predominating manifestation suggesting acute peripheral vestibulopathy. Small artery disease is the leading etiology of lateral pontine infarcts. Prognosis is usually favorable: over 80% of patients are independent [1, 2].

Table 1. Uncommon manifestations of pontine infarcts

Paramedian territorial infarcts
Contralateral pure supranuclear facial palsy
Unilateral hyperhidrosis, pure or associated with hemiparesis
Variants of one-and-a-half syndrome (eight-and-a-half syndrome; sixteen-and-a-half syndrome associated with ipsilateral supranuclear facial palsy)
Body lateropulsion, pure or associated with INO
Transient bilateral upbeat nystagmus associated with ataxia, INO and hemiparesis
REM sleep behavior disorder; periodic limb movements during sleep
Millard-Gubler syndrome: ipsilateral facial palsy and contralateral hemiplegia
Foville's syndrome: ipsilateral facial paralysis, conjugate gaze paralysis and contralateral hemiparesis
Lateral territory
Gasperini syndrome: ipsilateral abducens palsy plus complete anterior inferior cerebellar artery syndrome
Posterior territory
Marie-Foix syndrome: homolateral cranial nerve palsies, Horner's syndrome, hemiataxia, uvulo-palato-pharyngeal myoclonus, and contralateral spinothalamic sensory loss
Combined anteromedial and anterolateral territories
Raymond-Cestan syndrome (ipsilateral INO, contralateral hemiparesis and hemihypesthesia)
Bilateral infarcts
Peduncular hallucinosis: paramedian rostral pontine infarcts [8]
Freezing of gait: bilateral pedunculopontine nuclei infarcts
Fifteen-and-a-half syndrome (one-and-a-half syndrome with facial diplegia)
Bilateral horizontal gaze palsy and peripheral facial palsy
Hypesthesia in perioral area, hands and distal arms: bilateral tegmental infarcts at the caudal pons

Posterior Infarcts (Dorsomedial)

This territory is supplied by long circumferential branches of the superior cerebellar artery or anterior inferior cerebellar artery. Isolated infarcts of the extreme lateral pons are extremely rare, often occurring with concomitant cerebellar infarcts or more widespread brainstem infarctions due to BA occlusion [1, 2].

Bilateral Infarcts

These are most often part of extensive brainstem ischemia and account for up to 10% of all isolated pontine infarcts. Acute pseudobulbar palsy, bilateral motor deficits and tegmental dysfunction (neuro-ophthalmologic, sensory deficits and cranial nerve palsies) are usual findings. Bilaterally restricted ventral infarcts at the middle and caudal level can produce disturbed consciousness, locked-in syndrome, and diverse patterns of motor deficit (tetraplegia, triparesis, paraplegia and ataxic tetraparesis), sometimes as isolated features [1, 2].

Combined Infarcts

Large ventromedial infarcts (anteromedial and anterolateral territories) produce severe hemiparesis and dysarthria, whereas small infarcts manifest as DCHS, AH and PMH. Crural monoparesis

predominates in combined anterolateral and dorsolateral infarcts at the rostral level.

Pontine Hemorrhages

One in ten non-traumatic intracerebral hemorrhages is located in the pons. Chronic arterial hypertension is the leading etiology; less common causes are all types of vascular malformations, hematologic disorders, tumors and drugs [5]. Sudden onset, headache, vomiting and loss of consciousness occur particularly in large hemorrhages [6]. Large central hematomas usually extend to the rostral midbrain and the fourth ventricle, often beginning at the junction between the basis pontis and tegmentum and leading to loss of consciousness, quadriplegia, cranial nerve dysfunction, small and reactive pinpoint pupils, skew deviation, absence of horizontal gaze movements and ocular bobbing. Apneustic respiration or Cheyne-Stokes pattern, hyperthermia (comatose patients) and contralateral hyperhidrosis in the subacute phase may be seen. Unilateral basal or tegmentobasal paramedian hemorrhages may present with PMH or AH with dysarthria. Sensory deficits, ataxia and oculomotor abnormalities (INO, one-and-a half syndrome, horizontal gaze palsies and ocular bobbing) are common findings with hemorrhages restricted to the lateral tegmentum. Reports of sensory alien hand phenomenon are uncommon [7] (table 1). Isolated symptoms such as PMH, pure sensory stroke, oculomotor disorders (lateral gaze palsy of the supranuclear type, INO and one-and-a half syndrome), isolated abducens and facial palsies, and pure trigeminal sensory neuropathy have been reported with minute hemorrhages. Massive pontine hemorrhages have the worst prognosis, with death usually occurring in the first 48 h. Small tegmental hematomas have the best prognosis.

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Medullary Infarcts and Hemorrhages

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Abstract

Even though advances in noninvasive imaging of the brain have simplified the diagnostic of medullary strokes, clinical recognition can be still challenging. This chapter describes typical as well as rare clinical manifestations of medullary strokes to help clinicians' recognition of this rare but potentially life-threatening disease. It also contains imaging information useful to identify areas likely to be affected by strokes with resulting distinct syndromes.

Medullary syndromes are also called alternating syndromes implying localization to the brainstem due to the presence of crossed neurological signs, which usually include ipsilateral cranial nerve signs and contralateral signs of the ascending and descending tracts. However, besides well-described signs (i.e. clinical triad of medial medullary syndrome), patients with medullary strokes may also present a broad spectrum of untypical and even life-threatening features often unrecognized by clinicians [1–9]. The aim of this chapter is to outline various clinical features of medullary strokes and to provide imaging information useful to identify areas likely to be affected by strokes with resulting distinct syndromes.

Anatomy and Vascular Supply

The medulla can be classified into three major portions: the anterior portion, that contains fibers of the corticospinal tract which most of them cross over to the contralateral side; the tegmentum, which accommodates the olivary complex, nuclei of cranial nerves (VIII–XII, and part of V), parts of the reticular formation and ascending and descending fiber tracts (e.g. sympathetic fibers), and the posterior portion, which lower part is anatomically similar to the spinal cord and contains ascending fiber tracts that mostly end in the nuclei gracilis and cuneatus (fig. 1). The upper part of the posterior surface of the medulla also forms the lower floor of the fourth ventricle which contains the area postrema [10, 11].

The caudal regions of the medial medulla are supplied by paramedian branches of the anterior spinal artery (which arises from both vertebral arteries), whereas more rostral located regions of the medial medulla are supplied by paramedian branches of the vertebral arteries [10]. The lateral medulla is mostly supplied by circumferential (penetrating) branches from the vertebral artery (VA), while the posterior inferior cerebellar artery (PICA) supplies the remaining lateral and posterior portion of the medulla (fig. 1).

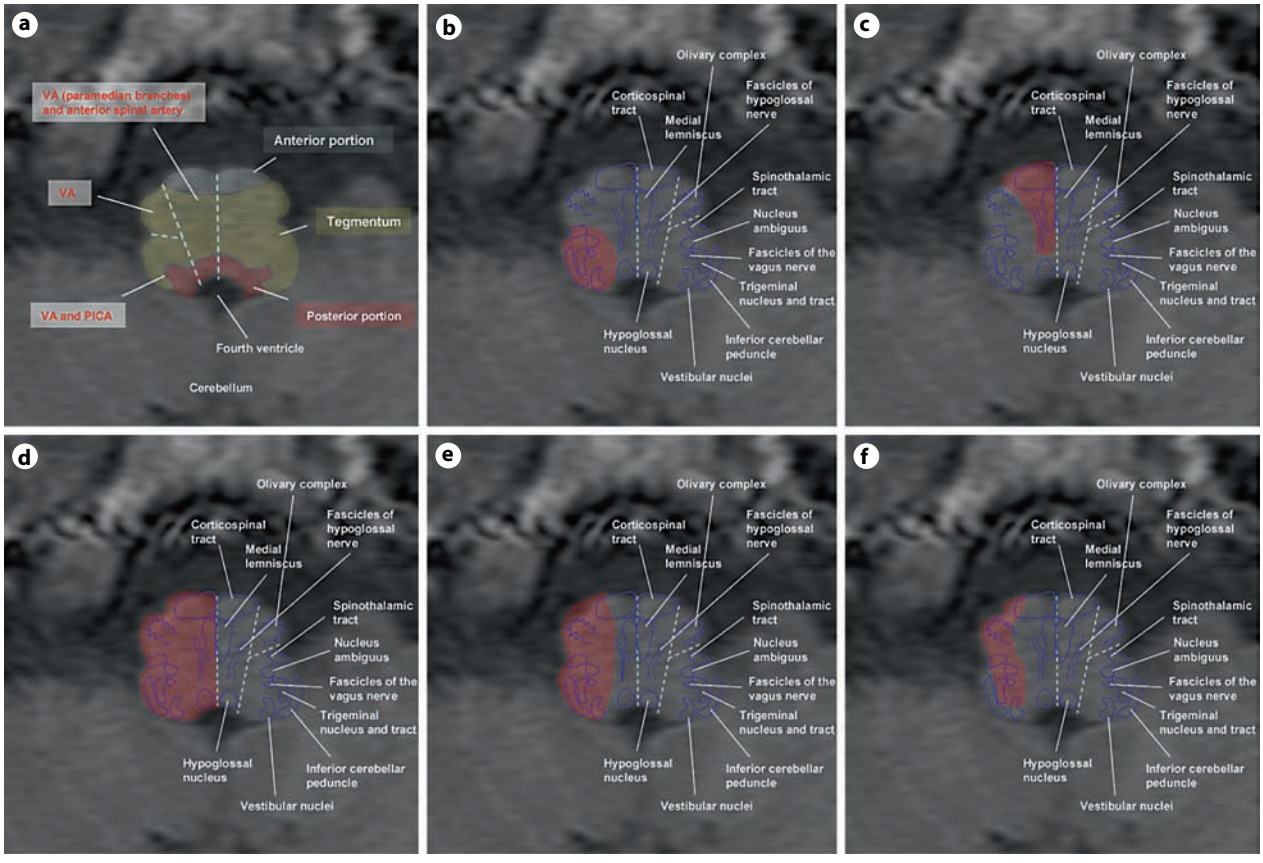

Fig. 1. Axial T_1-weighted MRI: cross-sectional slices of the middle medulla oblongata with superimposed schematic drawings showing (**a–f**) anatomical regions (colored areas) and vascular territories (dashed lines); (**b**) lesion of a lateral medullary syndrome; (**c**) medial medullary syndrome; (**d**) hemimedullary syndrome; (**e**) Babinski-Nageotte's syndrome, and (**f**) Cestan-Chenais syndrome (modified from Krasnianski et al. [15]).

Medullary Syndromes

Essentially, two vascular medullary syndromes can be distinguished: the lateral medullary syndrome (Wallenberg's syndrome), which is the most common syndrome (about 2% of ischemic strokes), and the medial medullary syndromes (Dejerine's syndrome) with an incidence up to four times lower than the lateral medullary syndrome. Spreading of an ischemic lesion and occlusions of several VA branches may uncommonly result in different but overlapping clinical syndromes: the hemimedullary syndrome (Reinhold's syndrome), in which clinical signs of both the medial and lateral syndromes occur simultaneously, the Babinski-Nageotte syndrome and the Cestan-Chenais syndrome [12–21]. Atherosclerotic disease of the intracranial VA and its branches are the major causes for medullary strokes but arterial dissection of the VA and embolism could also play a significant role.

Primary medullary hemorrhage is much less common than other brainstem hemorrhages and only a few cases have been described in the literature so far [22–26]. It has been shown to be

Table 1. Clinical medullary syndromes and symptoms (syndromes may occur complete, incomplete, and in combination with other medullary syndromes)

Clinical manifestation	Lesion localization/vascular supply	Common symptoms – affected structure(s)	Rare symptoms – affected structure(s)
Lateral medullary syndrome (Wallenberg's syndrome)	Dorsolateral medulla/VA (and PICA)	Ipsilateral facial decreased pain and temperature sensation – trigeminal spinal tract and nucleus	Ipsilateral facial pain (post-stroke onset, predominantly V1) – trigeminal spinal tract and nucleus
		Contralateral body decreased pain and temperature sensation – spinothalamic tract	Headache – trigeminal spinal tract and nucleus?
		Dysarthria – nuclei and tracts of CN IX, X, XII; nucleus ambiguus	Contralateral hemiparesis (not typical component; indicates a wider zone of ischemia) – corticospinal tract (see Babinski-Nageotte's syndrome)
		Vertigo/dizziness – vestibular nuclei	Ipsilateral facial palsy – aberrant corticobulbar tract in the upper medulla
		Nausea/vomiting – vestibular nuclei/area postrema	Hiccup – unknown
		Ipsilateral Horner's syndrome (may be incomplete; ptosis > miosis > anhidrosis) – descending sympathetic fibers	Contralateral tongue palsy – corticonuclear fibers
		Ipsilateral gait and limb ataxia - inferior cerebellar peduncle	Oculomotor disturbances (vertical or oblique diplopia, crossed diplopia, skew deviation, ocular tilt reaction, etc.) – nucleus prepositus hypoglossi, medial longitudinal fascicle, vestibular nuclei
		Horizontal or rotatory nystagmus (with the quick component moving towards the side of the lesion) – vestibular nuclei	Ipsilateral hemiparesis (Opalski syndrome) – ipsilateral corticospinal tract below the level of the pyramidal decussation?
		Dysphagia – nuclei and tracts of CN IX and X; nucleus ambiguus	Central respiratory dysfunction – solitary tract and nucleus, (dorsal and ventral) respiratory groups
		Diminished pharyngeal reflex - nuclei and tracts of CN IX and X, nucleus ambiguus	Central vasomotor dysfunction – solitary tract and nucleus, central sympathetic vasomotor fibers, nucleus ambiguous

Table 1. Continued

Clinical manifestation	Lesion localization/vascular supply	Common symptoms – affected structure(s)	Rare symptoms – affected structure(s)
Medial medullary syndrome (Dejerine's syndrome)	Medial medulla/ paramedian branches of vertebral and anterior spinal arteries	Contralateral hemiparesis – corticospinal tract Contralateral body decreased proprioception and vibration – medial lemniscus	Ipsilateral tongue palsy – CN XII nucleus or hypoglossal nerve fibers or fascicles
Hemimedulla syndrome (Reinhold's syndrome)	Hemimedulla/VA	Constellation of clinical symptoms of both the lateral and medial medullary syndrome; hemiparesis may be ipsi- or contralateral (depending on the localization of the lesion)	
Babinski-Nageotte's syndrome	Intermediolateral medulla/VA (and PICA) and anterior spinal artery	Lateral medullary syndrome plus contralateral hemiparesis (due to an extension of the lateral lesion to the more caudal located corticospinal tract ('Wallenberg with hemiparesis')	
Cestan-Chenais syndrome	Intermediolateral medulla/VA (and PICA) and anterior spinal artery	Symptoms of the Babinski-Nageotte's syndrome except ipsilateral cerebellar ataxia (due to sparing of the inferior cerebellar peduncle)	

associated with anticoagulant treatment, vascular malformation, and arterial hypertension, yet in most cases the mechanism remains undetermined. The clinical symptoms of medullary hemorrhage are poorly delineated. Headache is a common initial symptom and further clinical presentation may simulate various clinical symptoms that correspond to medial and lateral medullary involvement. Even though cardiac and respiratory disturbances have been also reported in medullary hemorrhages, the prognosis seems to be better than in more upper brainstem hemorrhages [25].

Conclusion

We summarize common and rare medullary syndromes as well as corresponding affected structures that should aid clinicians being aware of varied and sometimes unusual presentations of medullary strokes (table 1; fig. 1). In reality, clinicians often see symptoms attributable to different syndromes since thromboembolism to the terminal vertebral and basilar arteries can produce multilevel ischemia and more severe presentation than classic alternating syndromes. Nonetheless, the knowledge of these classic signs will help to suspect the most misdiagnosed type of stroke, i.e. those occurring in the posterior circulation.

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Cerebellar Infarcts and Hemorrhages

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Abstract

Cerebellar infarction accounts for about 3.4% of all ischemic strokes. Cerebellar syndromes are principally characterized by cerebellar symptoms and signs which depend on the involved vascular territories. In the Perugia Stroke Registry, infarct areas have included the superior cerebellar artery region in 36% of patients, the anterior inferior cerebellar artery region in 12%, and the posterior inferior cerebellar artery region in 40%; 12% of patients have had multiple vascular region involvement. 50% of the patients have had concurrent brainstem infarcts. Cerebellar hemorrhage accounts for about 10% of all intracranial hemorrhages and about 10% of all cerebellar strokes. Both stroke types can be worsened by complications due to a significant mass effect and brainstem compression. These events can lead to clinical deterioration which induces stupor and coma with a very high fatality rate.

Cerebellar stroke is an often misdiagnosed clinical condition that is potentially worsened by serious complications such as edema and brainstem compression. Principal clinical manifestations include dizziness, gait instability, headache, nausea and vomiting, all of which are non-specific and usually caused by more common and benign non-vascular disorders. Moreover, the neurological examination that explores cerebellar functions such as eye movement and coordination is often overlooked in first line clinical evaluation [see 1–3].

Outlines on Cerebellum Anatomy and Vascularization

The cerebellum is located in the posterior cranial fossa and is composed of a central part, the vermis, and two lateral expansions, the hemispheres. It is divided into a flocculonodular lobe which is located posteriorly and a more anterior corpus cerebelli. The corpus is further subdivided into anterior and posterior lobes. The outer layer of the cerebellum is gray matter while the inner layer is white matter called the arbor vitae. Deep into the arbor vitae of each hemisphere are the deep cerebellar nuclei, the fastigial, embolifom-globose and dentate nuclei; these give rise to the major efferent projections of the cerebellum. Three cerebellar peduncles, inferior, middle, and superior, connect the cerebellum to the brainstem and contribute to the walls of the fourth ventricle.

Three pairs of major arteries supply the blood to the cerebellum. The superior cerebellar artery (SCA) originates near the top of the basilar artery and perfuses the superior cerebellar peduncle and the tentorial surface of the cerebellum. The anterior inferior cerebellar artery (AICA) arises from

the lower basilar artery and supplies the middle cerebellar peduncle, the flocculus and the petrosal surface of the cerebellum. The posterior inferior cerebellar artery (PICA) originates from the vertebral artery and supplies the inferior cerebellar peduncle and the suboccipital surface of the cerebellum up to the great horizontal fissure. All these three pairs of arteries have proximal branches which supply blood to the lateral part of the brainstem. Thus, brainstem signs are highly common in cerebellar stroke.

Epidemiology and Pathogenesis of Cerebellar Infarction

In the Perugia Stroke Registry, as in other epidemiology studies, it is reported that cerebellar infarction accounts for about 3.4% of all ischemic strokes with a mean patient age of 72 years and prevailing in males with a ratio of 3:1 compared to females. Cerebellar infarctions are unilateral in 86% of the patients and bilateral in 14%. Bilateral cerebellar infarcts are significantly more frequent in patients with embolism than in patients with thrombosis. Infarct areas include the SCA region in 36% of patients, the AICA region in 12%, and the PICA region in 40%; 12% of patients have multiple vascular region involvement. 52% of the patients have concurrent brainstem infarcts.

Of cerebellar infarctions, 41% are associated with large artery atherosclerosis; 24% small artery disease, 9.8% cardioembolic, 7.3% other etiologies where the leading cause of stroke is vertebral artery dissection. Less common disorders associated with cerebellar stroke include migraine, vasculitis, hypercoagulable states and drug abuse. In 17% of cases the etiology remains undetermined.

Clinical Features

Cerebellar syndromes are principally characterized by different cerebellar symptoms and signs that group together depending on the involved vascular territories. Dizziness occurs in about three-quarters of cerebellar stroke patients with an impairment in spatial perception and stability that usually lasts for days. Gait instability is present in nearly half of the patients and this can be so severe that the patients are unable to walk; otherwise patients with cerebellar stroke tend to walk with a wide-based, staggering gait that cannot be fully corrected by visual feedback. Ataxia is often associated with a lateropulsion to the side of the lesion.

Nausea and vomiting can be leading symptoms in cerebellar stroke patients, present in up to 50% of cases, and can predominate the associated dizziness. Headache can be present in up to 40% of patients; the pain is usually located in the occipital/nuchal regions and is homolateral to the infarct. Limb ataxia is a less sensitive and specific cerebellar sign than commonly thought. In fact the inability to perform smoothly coordinated voluntary movements can be absent in 40% of cerebellar stroke patients and can be present in supratentorial stroke, especially in thalamic and basal ganglia infarctions as in ataxic hemiparesis. Patients more frequently overshoot the target (hypermetria) and oscillatory movements that become more prominent as the limb approaches the target can appear (frenage).

Dysarthria is present in nearly 50% of cerebellar strokes and can be observed with involvement of speech articulation and/or coordination impairment. Specifically, these can lead to an increased separation of syllables known as scanning speech. Nystagmus is observed in about 50% of patients and can assume different features. Vertical nystagmus is usually of cerebellar or pontomedullary origin. Other frequent abnormalities include an impairment of smooth pursuit eye movement that causes saccadic pursuit and the tendency to over- or undershoot the visual target on attempted fixation (saccadic dysmetria).

Superior Cerebellar Artery Occlusion

Fifty to 65% of cerebellar infarctions involve the SCA. Isolated SCA infarction rarely occurs because

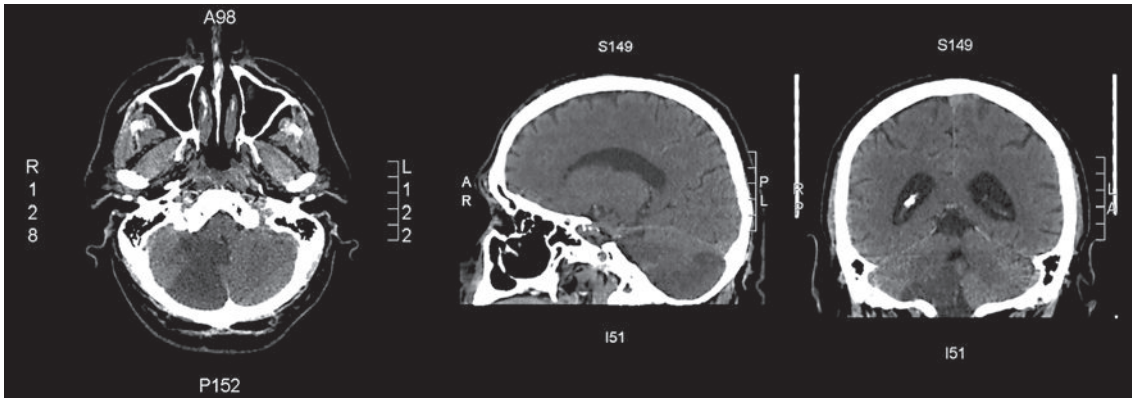

Fig. 1. Infarction in the territory of right PICA.

it is usually a consequence of a top of the basilar artery occlusion. SCA syndrome includes ipsilateral limb ataxia, ipsilateral Horner's syndrome, contralateral loss of pain and temperature sensibility of the face, limbs and trunk, contralateral fourth cranial nerve palsy. Brainstem symptoms and signs are related to the arterial branches of the SCA that supply the posterior-lateral area of the upper pons which includes the superior cerebellar peduncle, lateral lemniscus, spinothalamic tract, corticotegmental tract, descending sympathetic tracts, mesencephalic trigeminal tract and the root of the fourth cranial nerve. Frequently, with a concomitant top of the basilar artery occlusion, infarction can occur unilaterally or bilaterally in the occipitotemporal lobes, thalamus, subthalamic areas, and mesencephalon. Isolated occlusion of the lateral branch of the SCA can occur. The lateral SCA syndrome includes ipsilateral limbs dysmetria, ipsilateral axial lateropulsion, dysarthria, and gait unsteadiness. Similarly, an involvement of the lone medial branch of SCA can cause a dorsomedial SCA infarction with a clinical manifestation that includes unsteadiness of gait and dysarthria.

Anterior Inferior Cerebellar Artery Occlusion

Infarctions in the AICA territory are quite rare and often misdiagnosed. They are clinically characterized by vertigo, vomiting, dysarthria, ipsilateral limb dysmetria, ipsilateral facial palsy, ipsilateral tinnitus and hearing loss, ipsilateral Horner's syndrome, ipsilateral trigeminal sensory loss, contralateral temperature and pain sensory loss in the limbs and trunk. Ipsilateral conjugate lateral gaze palsy can be a consequence of an involvement of the flocculus, while dysphagia can be due to an extension of the infarction to the superior part of the lateral medulla and a contralateral limb weakness can be observed when the corticospinal tract in the pons or mesencephalon is involved.

Posterior Inferior Cerebellar Artery Occlusion

PICA occlusions are as frequent as SCA occlusions. This type of infarction can result from either a direct involvement of the PICA or from an occlusion of the vertebral artery (fig. 1). PICA syndrome is characterized by vertigo, headache, vomiting, dysarthria, ataxia with ipsilateral lateropulsion, ipsilateral limb dysmetria and nystagmus. Impairment of consciousness may occur in up to 50% of patients. More than half of patients evidence an associated brainstem infarction with a dorsal lateral medullary syndrome, known as Wallenberg syndrome. Here, the cerebellar symptoms and signs can be accompanied

by ipsilateral ninth and tenth cranial nerve palsy, ipsilateral Horner syndrome, loss of temperature and pain sensory on the ipsilateral face, contralateral temperature and pain sensory loss of limbs and trunk.

Isolated involvement of the medial branch of PICA can occur presenting with vertigo and ipsilateral axial lateropulsion. Infarctions with occlusion of the lateral branch of PICA can present with isolated dysmetria.

Diagnostic Studies

Even if cerebellar symptoms and signs can be quite sensitive and specific, clinical diagnosis of cerebellar stroke can be difficult. First-line examinations include neuroimaging to obtain evidence of a vascular origin of the symptoms, exclude an alternative non-ischemic origin, ascertain the underlying vascular mechanism of the event and identify prognostic outcome categories. Computed tomography (CT) scan is the most commonly used brain imaging test in an emergency setting given that it is widely available, quick to use and accurate at detecting acute hemorrhages. However, it has a low sensitivity for small lesions in the posterior fossa and tends to be negative in the first hours after stroke onset.

Magnetic resonance imaging (MRI) with diffusion-weighted imaging is more sensitive than CT scan in the acute phase, has a better accuracy for studying posterior fossa and with magnetic resonance angiography (MRA) a vascular evaluation without contrast medium can be performed. On the other hand, MRI is less diffused than CT, it takes longer to acquire images and needs patient collaboration thereby limiting a widespread application in the acute management. After confirming a diagnosis of cerebellar infarction, the vertebrobasilar vascular system needs to be investigated. Doppler ultrasound non-invasively evaluates extracranial vertebral arteries and can detect indirect signs of intracranial vertebral artery or basilar artery obstructions. CT angiography (CTA) and MRA are better for defining vertebral, basilar and cerebellar arteries. Nonetheless, digital subtraction catheter angiography remains the gold standard but should be restricted to selective cases. MRI with fat suppression techniques is the most sensitive technique for visualizing the subintimal hematoma when a vertebral artery dissection is suspected. For determining the etiology of cerebellar stroke, electrocardiography and echocardiography should be performed for identifying cardioembolic sources.

Treatment

The acute management does not differ from generic acute ischemic stroke treatment with some exceptions regarding the thrombolytic therapy. Indeed, most of the studies on intravenous alteplase in acute stroke had included patients with infarcts of the anterior circulation and its use in vertebrobasilar stroke is supported by only small-sized case series and a few larger cohorts. In the case of documented basilar artery occlusion, intra-arterial thrombolysis can be considered with a therapeutic window extendible up to 12 h. Suboccipital craniectomy should be considered in the case of pronounced edema with brainstem compression. This occurs in up the 20% of cerebellar infarctions with a peak on the third day. External ventricular drainage should be considered if an obstructive hydrocephalus occurs.

Cerebellar Hemorrhage

Cerebellar hemorrhage accounts for about 10% of all intracranial hemorrhages and for about 10% of all cerebellar strokes. This generally occurs in one of the hemispheres and involves the deep territory near the dentate nucleus originating from the distal branches of the superior or the posterior-inferior cerebellar artery. In 5% of cases cerebellar hemorrhage originates from the vermis. Regarding etiology, hypertension is the leading

cause, while anticoagulation, arteriovenous malformation, cavernomas, metastatic tumors, coagulopathy and trauma are other frequent causes.

Clinical features are the same as those listed above for cerebellar infarction. Acute posterior headache can more frequently be the onset symptom in cerebellar hemorrhage compared to cerebellar infarction but the lack of significant clinical differences makes CT essential for diagnosis. Cerebellar hemorrhage >3 cm can have a significant mass effect with brainstem compression. This event leads to a clinical deterioration that can induce stupor and coma with a very high fatality rate. Obstructive hydrocephalus can be a further complication. When brainstem compression symptoms and signs become evident or hydrocephalus is shown on CT, surgical treatment is recommended.

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Extended Infarcts in the Vertebrobasilar Territory

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Abstract

Posterior circulation stroke accounts for about 20% of all ischemic strokes in a variety of syndromic pictures ranging from lacunar and limited infarcts to more extensive involvement. Furthermore, infarcts in the vertebrobasilar (VB) region are frequently multiple and not univocally identifiable in one single clinical entity; the prognosis is sometimes unpredictable and very often is unfavorable having a high early mortality rate. The basilar artery (BA), which is the main vessel of the posterior circulation, supplies most of the brainstem and occipital lobes and part of the cerebellum and thalami, its occlusion (BAO) is the most severe occurrence in the posterior circulation infarct context. The optimum management of BAO is still under debate and in the absence of randomized studies the most appropriate approach is still unclear. In the previous chapters, single territory infarcts involving the posterior circulation have been discussed. The present chapter will discuss extended infarcts in the VB territory due to different degrees of VB involvement or to BAO.

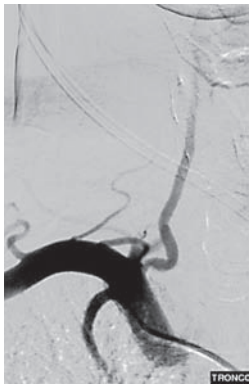
Etiopathogenesis

Atherothrombosis (fig. 1) is the most common cause of infarcts in the vertebrobasilar (VB) territory followed by embolic mechanism either from a distal source (cardiac, aortic arch) or from the same vascular region, especially in case of multiple posterior circulation infarcts. Generally, the middle portion of the basilar artery (BA) is often involved in atherothrombotic lesions, whereas proximal or distal occlusion are embolic.

Atherothrombotic lesions commonly present in the intracranial part of the vertebral arteries (VAs) are frequently occlusive and often bilateral [1]. Patients have often multiple vascular risk factors and present concomitant severe lesions within the anterior circulation; they often show extensive collateral views from the anterior circulation via the posterior communicating arteries, the anterior spinal artery and the leptomeningeal arteries [2–4]. Finally, dissection represents a possible infarct mechanism, its occurrence in the VB circulation is about 0.97/100,000 average annual incidence, mostly interesting the VAs and only secondarily the BA [5].

Clinical Features

VB vascular syndromes include a variety of different clinical pictures with not always typical syndromic features, their manifestation and outcome, as a consequence, are mostly related to the topographic location, the number and the extension of the lesions (fig. 2–5). Besides, it is possible to identify different topographic patterns in continuous or contiguous lesions corresponding to a single vascular territory and multiple and distinct



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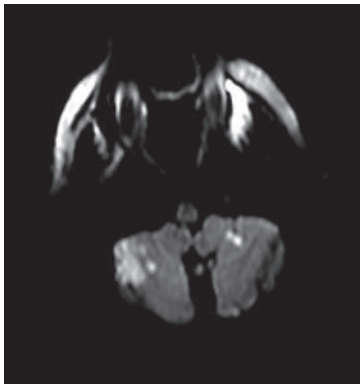

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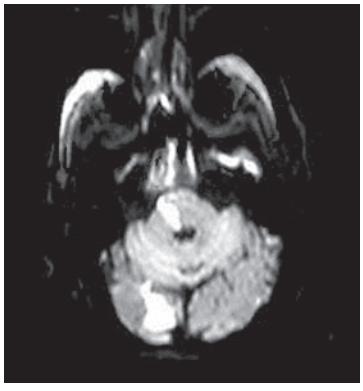

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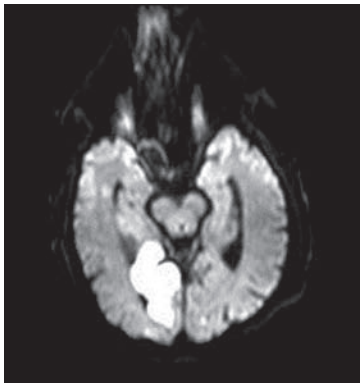

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Fig. 1. Right VA stenosis at origin.
Fig. 2. MRI DWI cerebellar lesion in BAO.
Fig. 3. MRI DWI pontine-occipital lesions in BAO.
Fig. 4. MRI DWI cerebellar lesion in BAO.

lesions corresponding to different vascular territories [6].

Up to 50% of patients with acute VB infarct present with transient ischemic symptoms from the same vascular territory during the days or weeks before, often with a 'waxing and waning' feature likely due to a reduced perfusion mechanism related to positional head changes or blood pressure reduction [7, 8]. Symptoms usually reflect vestibulocerebellar, motor and/or cranial nerve abnormalities [9]. Premonitory or progressive symptoms are usually suggestive of atherothrombosis, whereas an acute onset of symptoms, especially if corresponding to the middle or distal locations, is likely evocative of an embolic and unilateral intracranial VA occlusion [1]. The most vulnerable regions for reduced perfusion in patients with intracranial VA disease are the lateral medulla which is supplied by perforating arteries originating directly from the intracranial portion of the VAs and the PICA-supplied cerebellum. The main components of the vestibulocerebellar system, the vestibular nuclei and their connections with the vestibulocerebellar structures in the cerebellar vermis, are directly supplied by the intracranial VAs, explaining the frequency of premonitory, transient symptoms like vertigo and ataxia. Among cranial nerve-related symptoms, facial weakness or numbness and oculomotor abnormalities are dominant in cases of proximal BA involvement due to its supply of the lower brainstem tegmentum. The clinical syndromes of isolated mesencephalic, pontine or medullary ischemia have been presented in previous chapters.

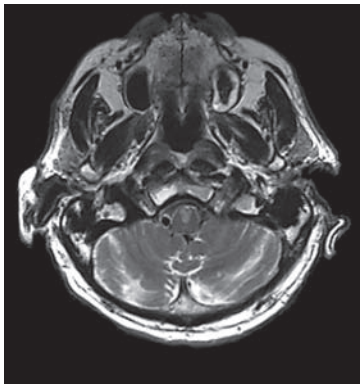
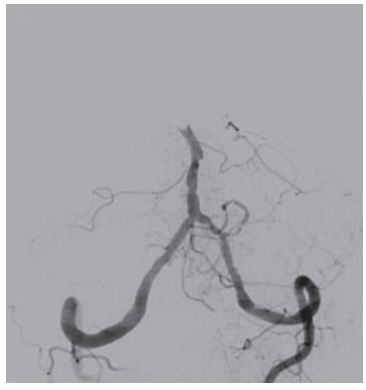
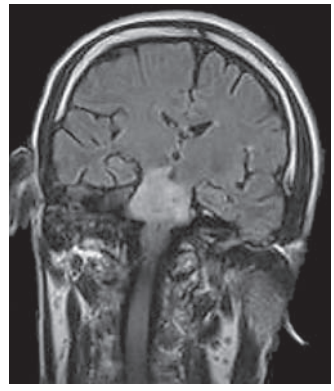

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Fig. 5. MRI T_2W bulbar lesion in a locked-in patient.
Fig. 6. Basilar artery occlusion.
Fig. 7. MRI FLAIR pontine lesion in a locked-in patient.

Extended or multiple infarcts in the VB territory may be due to bilateral VA atherothrombotic narrowing/occlusion, proximal BA stenosis/occlusion (BAO) or occlusion of major branches of the BA (including posterior cerebral artery) (fig. 6). Different topographic categories could be considered according to the vascular territory. Acute infarct in the posterior circulation may indeed affect: medulla, pons, cerebellum (posterior inferior/anterior/superior cerebellar artery territories), thalamus (posterior cerebral artery deep territory), occipital-temporal region (posterior cerebral artery superficial territory) and combined involvement [6]. The clinical features are those of multiple posterior territory or pontine infarcts. Premonitory spells and early clinical signs are often overlooked or misdiagnosed, they could be non-specific, although, if carefully evaluated, may represent crucial diagnostic clues to predict and even avoid the most catastrophic outcome such as BAO and subsequent infarct [10].

An identification criteria of clinicotopographic patterns of multiple acute posterior circulation infarcts corresponding to the vascular distribution is that proposed by the New England Medical Center Classification: proximal (medulla and posterior inferior cerebellar artery cerebellum fed by the intracranial VAs and their branches); middle (pons, lower midbrain, and anterior inferior cerebellar artery cerebellum fed by BA and branches), and distal (upper midbrain, thalamus, superior cerebellar artery cerebellum and temporal and occipital lobes fed by the distal BA and superior cerebellar artery, penetrating and posterior cerebral artery branches) [11].

Extensive infarction of the basis pontis (fig. 7) involving the pyramidal tracts brings to the devastating picture of the 'locked-in' syndrome [12]. This scenario indicates a state in which severe tetraplegia and cranial nerves palsy prevent the patient from any gestural and vocal communication despite spared consciousness and neuropsychological functions. The patient, tetraplegic, is fully alert and can only communicate by vertical eye movements. Prognosis is poor, mostly patients die within weeks or months, sometimes they live longer. BAO clinical onset may be classified as acute, gradual (progressive stroke) or preceded by prodromal symptoms [10].

Most common prodromal symptoms are vertigo and nausea (rarely isolated) (54–73%), focal motor weakness (facial droop, hemiparesis

or tetraparesis) (40–67%), dysarthria (30–63%), headache (40–42%), visual disturbances (diplopia) (21–33%), and confusion (17–33%). On admission, patients may present with a combination of the most common symptoms, they often have pupillary abnormalities and cranial nerve palsy, tetraparesis or tetraplegia are not always present, sometimes they have different degrees of consciousness impairment up to coma. Patients with oculomotor and motor symptoms, especially in the presence of alteration of consciousness, tend to have more BAO at all locations, alone or in combination with a VA occlusion, whereas vertigo and cerebellar symptoms suggest a VA lesion sparing the BA.

The first full description of BA thrombosis was by Kubick and Adams [13] who focused on a selected group of patients with BAO. Since then, although less homogeneous patient groups have been described, in terms of prognosis, it is of relevance to distinguish the VB territory infarcts sustained by unilateral from the bilateral VAs narrowing or occluding lesions and by BAO isolated or not. Patients with bilateral VA occlusion or BAO carry on a poor prognosis, while those with perforating vessels occlusion generally have a more benign evolution; nevertheless, there are exceptions to these clear-cut distinctions depending on the initial neurological impairment, risk factor profile and pathogenetic mechanisms and it is not uncommon that a minor vessel occlusion ends up with a severe neurological deficit [14].

Neuroimaging

The most rapid and cost-effective acute evaluation is unenhanced CT scan, however the posterior fossa assessment by CT is notoriously difficult although the presence of a hyperdense BA is considered a sensitive sign for acute thrombosis and can also be used to prognostically predict the short- and long-term outcome [15]. Computed tomography angiography has been shown to be highly accurate in detecting acute BAO, in alternative magnetic resonance angiography can also be used although it needs longer execution time and patient collaboration. Digital subtraction angiography represents the gold standard and allows both diagnosis and therapeutical intervention.

Treatment

The safety and efficacy of intravenous thrombolysis given 4.5 h from the onset of symptoms in acute ischemic stroke [16] and intra-arterial thrombolysis within 6 h [17] applies only indirectly to patients with acute VB occlusion because only a few of these patients were included in the trials and there were no specific treatment indications, also the time window remained undefined, considered well beyond the therapeutic window for the anterior circulation, and possibly because of slower progression of ischemic tissue damage. Certainly, in the absence of clear evidence of superiority of one therapeutical approach over the other, and in the real-life scenario, intravenous treatment should be encouraged in patients who present with acute symptomatic BAO and mild to moderate deficits; additional intra-arterial treatment might be considered in case of acute worsening. In every case, treatment should be initiated as soon as possible since there is no evidence about the most efficacious time window [18–20].

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Border-Zone and Watershed Infarctions

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Abstract

Border-zone (BZ) and watershed infarcts occur at the junction of two artery territories and are precipitated by a hemodynamic impairment although they cannot be excluded from microembolic etiology. These strokes may often be preceded by specifically precipitating circumstances that induce hypotension and/or hypovolemia (rising from a supine position, exercise, Valsalva's maneuver, administration of antihypertensive drugs, bleeding and anemia). Anterior BZ infarction occurs with a motor deficit of one or both contralateral limbs, associated with aphasia or mood disturbance. Campimetric disturbances are a constant feature of posterior BZ infarct associated with fluent aphasia and hemihypoesthesia. Subcortical and capsule-thalamic BZ infarctions often mimic lacunar syndrome due to small-vessel disease. Cerebellar BZ infarction is associated with non-specific vertigo syndrome or ataxia, while in brainstem BZ infarction patients are comatose with other signs of brainstem being compromised.

Brain circulation can be anatomically divided in two main systems: (1) *superficial*, which creates a network that surrounds the brain and forms anastomosis before sending perforating centripetal vessels, and (2) *deep*, with centrifugal vessels that penetrate the parenchyma and do not anastomose. At the junctions among three principal brain artery territories or between the superficial and deep branches of these arteries, a distal field ('last meadows') can be identified with so-called 'misery perfusion' in which cerebral blood flow, cerebral blood volume, perfusion pressure and fractional extraction of oxygen were significantly decreased [1]. These findings lead to a particular susceptibility to hemodynamic changes of brain circulation. Alternatively, is has been postulated that microembolism (from the heart or from the atherosclerotic artery plaque) can be a cause of border-zone (BZ) infarcts because microemboli preferentially propagate in boundary areas [2]. A unifying hypothesis suggests that hemodynamic BZ characteristics reduce the ability of blood flow to wash out emboli and then determine BZ susceptibility [3].

Ischemic lesions that do not occur in a well-marked area but at a junction of two (or three) artery territories are defined as *BZ infarcts* (terminoterminal infarcts), if they occur between arterial territories without arterial collateral circulation. If they occur between arterial territories with arterial collateral circulation, they are defined watershed infarcts (junctional infarcts). There are two distinct types of BZ: (1) cortical BZ (CBZ) between the cortical cerebral and cerebellar territories of the main brain artery and more likely to be involved in watershed infarct due to microembolism, and (2) internal BZ (IBZ) in the deep

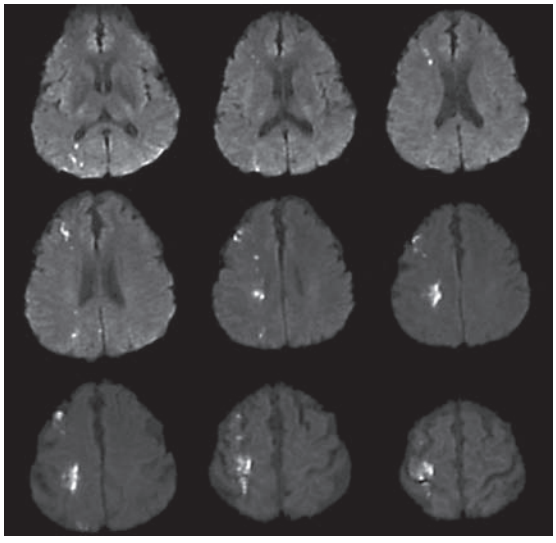

Fig. 1. Diffusion-weighted brain MRI showing anterior and posterior CBZ and IBZ infarcts.

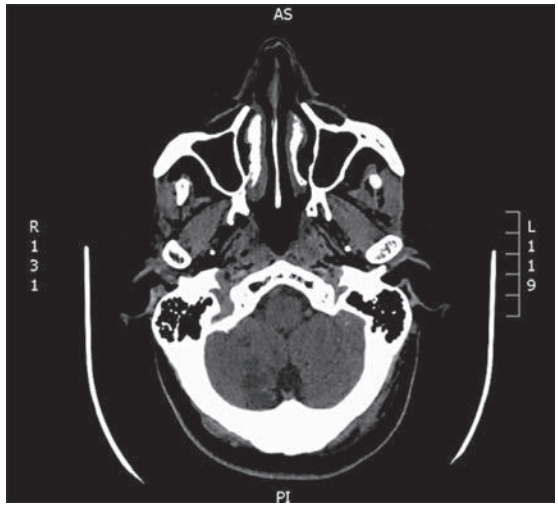

Fig. 2. CT scan showing cortical and subcortical cerebellar BZ infarcts.

cerebral or cerebellar white matter or in the brainstem and more likely to be involved in BZ infarcts underlined by a hemodynamic mechanism (fig. 1, 2). Cerebral CBZ are localized at the junction of the anterior cerebral artery (ACA) and middle cerebral artery (MCA), a thin frontal-parasagittal wedge extending from the anterior horn of the lateral ventricle to the frontal cortex, and at the junction of the MCA and posterior cerebral artery (PCA), a wedge extending from the posterior horn of the lateral ventricle to the parieto-occipital cortex. Cerebral IBZ are localized between the deep and cortical perforators of MCA-supplied territories, affecting the *corona radiata;* between the perforators of ACA- and MCA-supplied territories, affecting the *centrum semiovale*, and between the lenticulostriate artery (carotid branches) and thalamic artery (vertebrobasilar branches) supplied territories, involving the paramedian territory and inferior-lateral territory of the thalamus. In the infratentorial territory, at the junction of the posterior-inferior cerebellar artery (PICA) and superior cerebellar artery (SCA) territories, a CBZ can be localized affecting the cerebellar hemisphere and an IBZ affecting deep cerebellar white matter. In brainstem an IBZ can be localized between the paramedian perforators of the basilar arteries and lateral perforator of short circumferential branches of the cerebellar artery-supplied territories, involving the posterior-medial pons region.

Clinical Findings. Taking the history of stroke onset into consideration, there are some circumstances which are useful to suppose a BZ infarct, especially when hemodynamic mechanisms are involved. For example, symptoms can occur when rising from a supine or sitting position, physical exercise, consuming a meal, Valsalva's maneuver or coughing, during which cerebral blood flow decreases because it is redirected to other parts of the body. Also, systemic hypotension, caused by administration or an increase of antihypertensive drugs, or as collateral effect of other drugs, or during anesthesia, especially of cardiovascular surgery, and hypovolemia, caused by bleeding or anemia, should be considered as precipitant factors of

hemodynamic stroke [4]. The contemporary presence of carotid or vertebrobasilar artery obstruction seems to be a necessary condition by leading to silent hemodynamic impairment, negatively affected by precipitating circumstances. In some series, the frequency of internal carotid occlusion or tight stenosis rises to 75% [5].

At the onset of BZ stroke, loss of consciousness without focal symptoms is frequent, more so than in thromboembolic stroke. The patient often complains of a previous transient ischemic attack, with suggestive patterns, such as *opticocerebral syndrome* (simultaneous amaurosis and contralateral motor deficit, led by ischemia of the optic nerve and motor cerebral area) or *limb shaking* (involuntary movement of the contralateral arm or leg, without EEG epileptic activity correlates) [6]. Because of the high rate of cortical involvement, early-onset seizures are more frequent in watershed infarcts than in other types of stroke [7]. Another rare manifestation of carotid marginal perfusion is *retinal claudicatio* (monocular transitory blindness after bright light exposure, with an increased metabolic demand of the retina that cannot be met) [8]. A mild global cognitive impairment can be caused by chronic hypoperfusion.

Anterior BZ strokes, between ACA and MCA territories, typically develop with contralateral motor impairment, sparing facial muscles. When the lesion is prevalently cortical, the upper limb is more affected. The deficit can be distal, of the wrist and the hand, and initially mistaken for peripheral radial palsy, or can be proximal, of the shoulder [9]. When this territory is bilaterally involved, it is referred to as the 'man-in-the-barrel' syndrome, with limitation of arm movements but sparing the capacity to walk. When the lesion is subcortical, the lower limb is prevalently affected and, if bilateral, it is referred to as 'pseudo-spinal' syndrome and can be misdiagnosed as spinal cord involvement. In patients with left-side stroke, transcortical motor aphasia (non-fluent, with preserved repetition and comprehension) is usually present as a consequence of disconnection of Broca's area and the motor supplementary area. When an infarct is localized in the right hemisphere, mood disturbances, such as apathy or euphoria, can occur. In some cases, apathy can be so deep, leading to a clinical picture of akinetic mutism (lack of spontaneous thought, speech and motor activity, but without impairment of memory or motor pathways caused by loss of frontal executive functions) [10].

Posterior BZ infarctions, between MCA and PCA territories, typically develop with a campimetric deficit, homonymous lower quadrantopsia or hemianopsia caused by interruption of optical radiations. When the stroke is bilateral a complex visual impairment can occur such as cortical blindness (patients have no vision but non-cortical functions of the eyes are preserved so that the patient can distinguish light/dark and pupillary reflex is normal); Balint's syndrome (a triad of visuo-ocular symptoms including the inability to perceive simultaneous events in one's visual field – *simultanagnosia*, the inability to fixate and follow an object with eyes – *optic apraxia*, and the impairment of target-pointing under visual guidance – *optic ataxia*), and visual hallucinations. Cortical involvement of the left hemisphere can occur with phasic disturbances, such as Wernicke's aphasia (fluent aphasia with neologism, word salad and incorrect language content) when Wernicke's area is involved, or transcortical sensory aphasia (fluent aphasia, with poor comprehension, but good repetition) when infarction causes interruption of the connection between Wernicke's area and posterior parietotemporal-associative areas. While motor disturbances are absent or mild, sensory impairment for associative modalities may occur because of the interruption of connection between the primary sensory area and posterior-associative areas. Hemineglect and anosognosia may be present.

Subcortical hemispheric BZ infarct at the junction of deep and cortical perforators of MCA-supplied territories and capsular-thalamic BZ

infarct at the junction of lenticulostriate artery- and thalamic artery-supplied territories occur without a specific neurological picture but with motor stroke, with or without sensory loss, that mimics lacunar infarction due to small-vessel disease. There are less consistent data concerning infratentorial BZ infarct due to the difficulty of diagnosing this type of stroke in vivo. This difficulty is led, on the one hand, by great anatomic variations of cerebellar blood supply, and on the other by the small size of the brainstem. These seem to preclude a clinically reliable diagnosis at these levels. However, isolated cerebellar BZ infarct can occur with generic symptoms of vertigo, dizziness and gait ataxia, while BZ brainstem strokes usually occur with a severe clinical picture, characterized by a reduced level of vigilance and other signs of brainstem dysfunctions, such as gaze palsy. Finally, concerning the outcome, BZ and watershed infarcts had a higher death rate than other types of stroke (9.9 vs. 2.3% per year), being more frequently associated with severe heart disease with hypotension and with severe arterial stenosis. Managing this type of stroke is crucial to avoid or to treat all potential hemodynamic disturbances, especially heart disease [11].

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Acute and Chronic Carotid Occlusion Syndromes

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Abstract

Clinical manifestations of acute internal carotid artery (ICA) occlusion are the most variable among all cerebrovascular syndromes. This extreme variability is related essentially to three variables: collateral circulation, cerebral vasoreactivity with hemodynamic factors, and the characteristics of occlusion. Intracranial circulation is represented by a mirabilis network connecting both anterior-posterior and deep-shallow circulation systems. The compensation mechanisms in ICA occlusion can be influenced by preexisting risk factors. Moreover, an alteration in cerebral hemodynamic function related to previous stroke, chronic hypoperfusion and vascular risk factors play a relevant role in the clinical features of ICA occlusion. On the other hand, also after an acute event, the clinical evolution in a patient with ICA occlusion, which is defined here as chronic occlusion, is extremely variable: some patients remain asymptomatic, while others suffer recurrent TIA or minor/major stroke. The factors set forth above associated with other underlying conditions also affect clinical development. However, a fundamental role is played by the proper management of vascular risk factors whether in acute or chronic ICA occlusion.

Occlusion of internal carotid artery (ICA) accounts for 6–15% of all acute cerebrovascular events [1, 2]. The clinical manifestations of ICA occlusion are the most variable among all cerebrovascular syndromes. Unlike other vessels the ICA is a terminal vessel due to its continuity with the vessels of the circle of Willis and those of the ophthalmic artery. Virtually no part of the brain is closely dependent on this route. For this reason, the clinical manifestations of cerebral ischemia in patients with ICA occlusion are the most variable. ICA occlusion remains silent in 30–40% of cases, but can also cause transient ischemic attack (TIA) as well as minor or major disabling stroke (fig. 1).

Clinical Features

Carotid TIA is most frequently represented by transient monocular blindness (TMB): Temporary loss of vision in one eye, also known as amaurosis fugax, may be considered a brief monocular visual obscuration described by the patient as a fog, blur, cloud, mist, and so forth. TMB can be accompanied by scotomas. The duration of visual impairment is usually <15 min and rarely exceeds 30 min. Most patients are affected for only 1–5 min. TMB may be caused by transient ischemia in the distribution of the ophthalmic, posterior ciliary, or central retinal artery (CRA). Ipsilateral hemispheric symptoms may be present. Vision is usually fully restored after an attack, although in a small number of patients permanent visual loss from retinal infarction is possible. Episodic attacks of fleeting

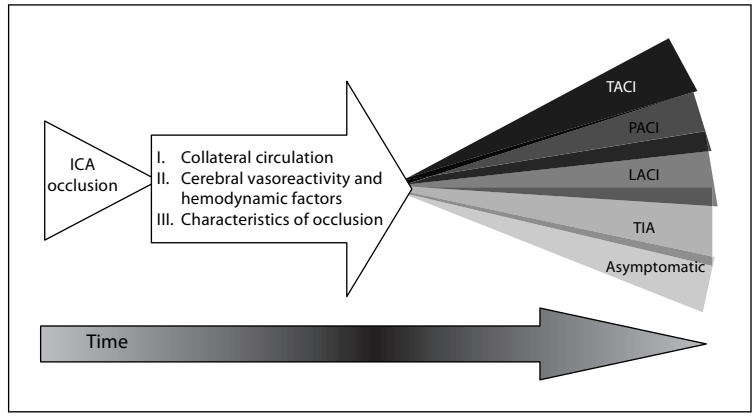

Fig. 1. Acute and chronic carotid occlusion syndrome. TACI = Total anterior cerebral ischemia; PACI = partial anterior cerebral ischemia; LACI = lacunar cerebral ischemia; TIA = transient ischemic attack.

blindness occur as arteriosclerotic plaques progressively narrow the lumen of the ipsilateral ICA, leading to periodic reductions in blood flow, reduced pressure in the ophthalmic artery, transient ocular ischemia, or vascular insufficiency. Often, cholesterol crystal or plugs of platelets (sometimes visible with ophthalmoscope) will detach from an ulcerating plaque in the vessel wall and embolize to distal branches of the carotid and ophthalmic arteries, the CRA, and/or the posterior ciliary arteries, without causing permanent visual loss. For this reason, TMB is regarded as one variety of carotid artery TIA, and like other TIAs, TMB is a warning of impeding stroke. TMB may be also the presenting symptom of ICA dissection in young or giant-cell arteritis affecting the elderly [3].

Acute monocular blindness: Sudden monocular blindness, excluding ophthalmic emergencies (detachment of the macula, acute closed-angle glaucoma, vitreus or macula hemorrhage and factitious visual loss), is the major symptom of an ocular stroke leading to permanent visual loss. Ocular stroke can be due to CRA occlusion, branch retinal artery occlusion or anterior ischemic optic neuropathy (AION) the latter which is the result of infarction of the optic nerve. The principal causes of CRA occlusion are: embolic, occlusion in situ due to thrombosis or hemorrhage into a plaque, arteritis (e.g. giant-cell arteritis, thromboangiitis obliterans and polyarteritis nodosa), vasospasm (e.g. migraine, Raynaud's disease) and hypoperfusion (e.g. high intraocular pressure due to glaucoma, low retinal blood pressure due to a severe ICA stenosis or severe hypotension). At fundus examination, the ischemic retina takes on a white ground-glass appearance, and the normal red color of the choroids showing through at the fovea accentuates the central cherry-red spot of the macula. Within days of the acute event, the retinal opacification, the cherry-red spot, and the nerve fiber-layer striations disappear, and optic atrophy of the optic disk develops. Branch retinal artery occlusion is usually due to an embolus at an arterial bifurcation in a branch of CRA. Symptoms are sudden and can lead to a permanent loss of a sector of the visual field, with retinal infarction corresponding to the vascular territory of the arteriole blocked. The principal causes of AION are: non-arteritic (commonly due to atherosclerosis, collagen vascular disease as SLE, severe hypotension, e.g. during surgical procedures, renal hemodialysis, hematological disorders as sickle-cell disease, polycythemia, thrombocytopenic purpura, leukemia and anemia), an arteritic variety due to giant-cell arteritis, and embolic occlusion, even if rare, of the posterior ciliary arteries as a complication of ipsilateral ICA disease or cardiac surgery. AION is an uncommon complication of ICA occlusive disease.

Severe loss of acuity is characteristic of the arteritic form of AION. In arteriosclerotic or embolic AION, partial infarction of the nerve may occur, with a preservation of central vision. The fundus examination reveals swelling of a segment or all of the optic disc which may be indistinguishable from that seen with raised intracranial pressure, pallor of the disc, flame-shaped hemorrhages near the disc and distended veins. Rarely does the ischemic optic neuropathy affect the nerve only proximal to the lamina cribrosa and manifest without disc swelling (posterior ischemic optic neuropathy). Finding episcleral vascular congestion, a cloudy cornea, neovascularization of the iris (rubeosis iridis) and a sluggishly reactive mid-dilated pupil indicates chronic anterior segment ocular ischemia which may be due to carotid occlusive disease.

In embolic ocular stroke both ischemic disk changes and an ambolus in a branch of CRA may be present. In ocular stroke, an amaurotic pupil (e.g. absence of constriction to light on direct illumination, intact consensual light response, and intact near-response) is present when the eye is completely blind. An afferent pupil defect (e.g. impaired direct-light response) is present if some vision is preserved. Rarely, patients with an acute ischemic stroke in the carotid territory also had ipsilateral optic nerve infarction (opticocerebral syndrome). In these cases, hemodynamic infarction was suggested by triggering by a drop in blood pressure, decreased ophthalmic artery flow and perfusion pressure, and cerebral infarction in a watershed area [4].

Stroke patients with ICA occlusion may present symptoms ranging widely from the most severe forms with total involvement of the anterior circulation (TACI) [5] to lacunar syndromes passing through complete or partial middle or anterior cerebral artery involvement. This extreme variability is related to the subtle balance of at least three variables (I. Collateral circulation; II. Cerebral vasoreactivity and hemodynamic factors; III. Characteristics of occlusion; cf. fig. 1) that interact closely with each other to determine the clinical and pathological features of cerebral ischemia.

Clinical Variability Factors

Collateral Circulation. Cerebral collateral circulation refers to the subsidiary network of vascular channels that stabilize cerebral blood flow when principal conduits fail. The arterial anatomy of collateral circulation includes extracranial sources of cerebral blood flow and intracranial routes of ancillary perfusion that are commonly divided into primary or secondary collateral pathways. Primary collaterals include the arterial segments of the circle of Willis, whereas the ophthalmic artery and leptomeningeal vessels constitute secondary collaterals. Interhemispheric blood flow across the anterior communicating artery and reversal of flow in the proximal anterior cerebral artery provide collateral support in the anterior portion of the circle of Willis. The posterior communicating arteries may supply collateral blood flow in either direction between the anterior and posterior circulations. Additional interhemispheric collaterals include the proximal posterior cerebral arteries at the posterior aspect of the circle of Willis. Considerable variability exists in the anatomy of the circle of Willis, with frequent asymmetry and an ideal configuration in only a minority of cases. Anatomic studies note absence of the anterior communicating artery in 1% of subjects, absence or hypoplasia of the proximal anterior cerebral artery in 10%, and absence or hypoplasia of either posterior communicating artery in 30% [6]. Reversal of blood flow within the ophthalmic artery may provide secondary collateral support. Anastomoses between distal segments of the major cerebral arteries also contribute ancillary collateral blood flow. Leptomeningeal and dural arteriolar anastomoses with cortical vessels further enhance the collateral circulation. The course and anatomic characteristics of collaterals may vary extensively, with atypical collaterals such as anterior choroidal supply from the posterior

circulation induced by pathophysiological conditions [7]. Following an acute ICA occlusion, distal perfusion deficits may be of interest to all or part of the middle cerebral artery territory, and when the anterior communicating artery is very small, it also affects the ipsilateral anterior cerebral artery territory. It is likely that the opening of collaterals depends on several compensatory hemodynamic, metabolic and neural mechanisms. Clinical observations further emphasize the pace of cerebral ischemia as a critical variable, with collateral capacity improving over time [8]. The efficacy of collateral vessels probably depends on age, duration of ischemia, and associated comorbidities. Chronic hypoperfusion due to arterial flow restrictions such as extracranial carotid stenosis or intracranial stenotic disease promotes collateral development. Secondary collateral pathways that require time to develop are presumed to be recruited once primary collaterals at the circle of Willis have failed. The hemodynamic effects of collateral circulation may be important in maintaining perfusion to penumbral regions, but these collateral vessels may also facilitate clearance of fragmented thrombus from more proximal locations [6–9]. Hemodynamic fluctuations may influence the endurance of collaterals, possibly threatening cerebral blood flow.

Cerebral Vasoreactivity and Hemodynamic Factors. When cerebral perfusion pressure (CPP) is normal (stage 0), cerebral blood flow (CBF) is closely matched to the resting metabolic rate of the tissue. As a consequence of this resting balance between flow and metabolism, the oxygen extraction fraction (OEF) shows little regional variation. Moderate reductions in CPP have little effect on CBF. Vasodilatation of arterioles reduces cerebrovascular resistance, thus maintaining a constant CBF (stage I). As a consequence, intravascular cerebral blood volume is elevated. This phenomenon is known as cerebrovascular autoregulation. With more severe reductions in CPP, the capacity for compensatory vasodilatation is exceeded, autoregulation fails, and CBF begins to decline. A progressive increase in OEF now maintains cerebral oxygen metabolism and brain function (stage II) [10, 11]. This more severe form of stage II cerebral hemodynamic failure has also been termed *misery perfusion* [12]. In ICA occlusion, distal perfusion pressure and CBF may remain normal if collateral circulatory pathways are adequate [13, 14]. If perfusion pressure is reduced distal to an occlusive lesion because of inadequate collaterals, CBF can be maintained at normal levels by autoregulatory dilatation of resistance vessels. This autoregulatory vasodilatation may be identifiable as a reduced or absent CBF response to vasodilatory stimuli such as hypercapnia or acetazolamide [13]. When the capacity for autoregulatory vasodilatation to maintain normal blood flow is exceeded, CBF falls relative to the cerebral rate of oxygen metabolism ($CMRO_2$), and OEF increases to maintain normal $CMRO_2$. While increased OEF has been shown to be a powerful independent risk factor for subsequent ischemic stroke in patients with symptomatic carotid occlusion, the majority of such patients still remain stroke-free [11]. There are several potential mechanisms by which the brain and cerebral vasculature could adapt to a chronic reduction in CBF relative to $CMRO_2$ in the absence of cerebral infarction. CBF may increase over time as collateral pathways develop [15]. Conversely, $CMRO_2$ may decrease and thus re-establish the balance between CBF and $CMRO_2$.

Characteristics of ICA Occlusion. Atherosclerosis is the most common etiology in ICA occlusion. Other causes are cardioembolism, dissection and radiation-induced vascular disease. Occlusion in acute cardioembolic origin that is inscribed on the brain with poor development of collateral circulation results in a dramatic event that leads to massive ischemic area with all symptoms. In the presence of embolism in ICA occlusion, many patients who had no obvious TIA prior to their stroke experienced a moderate to severe clinical deficit. In the patients without embolism many showed a widespread delay in cerebral artery perfusion, experienced a greater frequency

of TIA before their stroke and had a milder stroke than did those with embolism [16]. In case of ICA dissection (CAD) there is headache, neck pain, Horner syndrome, pulsatile tinnitus, cranial nerve palsy on the side of the ICA. Headache and neck pain were also important warning signs preceding the onset of stroke from a few minutes and 14 days in nearly 80% of patients [17].

Chronic Carotid Occlusion

After an acute event, the clinical evolution in a patient with ICA occlusion is extremely variable: some remain asymptomatic, others have recurrent TIA or minor and major stroke (fig. 1). The risk of subsequent stroke in patients with TIA or non-disabling stroke associated with ICA occlusion is between 5 and 6% per year. Even in this condition the variability of symptoms is linked to factors mentioned above, but also to possible underlying conditions as potential predictors of risk. For example the occurrence of previous TIAs could have promoted the development of collateral circulation, but also may have been a reason to control the vascular risk factors and initiate secondary prevention with antithrombotic treatment. Previous reports found watershed infarcts as predictors of recurrent stroke in patients with ICA occlusion [18]. Thromboembolism is an explanation for cerebral ischemia in patients with recurrent stroke post ICA occlusion from the thrombus in the ICA, from the external carotid artery, from the stump of the ICA, from the heart or from the aorta [18, 19]. Carotid stump syndrome is one of the recognized causes of recurrent cerebrovascular events after ICA occlusion. It is believed that microemboli arising from the stump of the occluded ICA or ipsilateral external carotid artery can pass into the middle cerebral artery circulation as a result of patent external carotid-internal carotid anastomosis and reversed flow in the ophthalmic artery. Another cause of clinical variability is represented by possible spontaneous recanalization. The recanalization of an occluded atherosclerotic ICA seems to be a rare event. The existence of very early spontaneous recanalization, within 1–2 h of onset has been reported. In patients with CAD, the recanalization process can occur between 2 days and 6 weeks after stroke. The frequency of recanalization has not been well established in the literature and appears to increase over time between the initial occlusion and follow-up examination. The degree of contralateral ICA stenosis did not seem to influence the risk of recurrent stroke [20, 21].

Conclusion

The acute and chronic clinical symptoms related to ICA occlusion are highly variable. This variability is linked to a subtle balance between several factors consisting of the activation of collateral circulation, the hemodynamic conditions of intracranial circulation and means of implementation of carotid occlusion. A key factor in this delicate balance is the correct management of vascular risk factors in terms of both primary and secondary prevention. In this perspective the future exhaustive interpretation of these subtle mechanisms may also further explain differences in clinical outcome and expand treatment options for stroke in acute and chronic ICA occlusion.

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Venous Ischemic Syndromes

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Abstract

Venous ischemic syndromes represent a rare type of cerebrovascular disease that more commonly affects young women. Because of the remarkable variability of clinical presentations and neuroimaging signs, these syndromes represent an important clinical challenge. The most common clinical presentations include headache, seizures, focal neurological deficits, altered consciousness, and papilledema, which can present in isolation or in association with other symptoms. According to the grouping of symptoms and signs, four main patterns have been identified: isolated intracranial hypertension, focal syndrome, cavernous sinus syndrome, and subacute encephalopathy. CT scan is commonly performed as the first-line diagnostic test, in most cases showing indirect signs such as cerebral edema, ischemic or hemorrhagic lesions, or signs of venous stasis. The most accurate diagnostic techniques to objectively confirm the diagnosis include magnetic resonance angiography and computed tomography angiography. Clinical presentations and neuroimaging signs are important predictors of outcome following venous ischemic syndromes. Coma, epileptic seizures and intracranial hemorrhage were shown, among others, to be independent predictors of poor outcome.

Venous ischemic syndromes represent a rare type of cerebrovascular disease occurring with an estimated annual incidence of 5–7 cases/million children and 3–4 cases/million adults, and thus accounting for 0.5% of all strokes [1]. Until a few years ago, systemic or local infections commonly affecting the superior sagittal sinus were identified as the commonest causes [2, 3], and the diagnosis was frequently obtained after autopsy [4]. More recent data show that venous ischemic syndromes are more prevalent in young female patients (female gender accounts for approximately 75% of the patient population), with gender-related risk factors being identifiable in about two thirds of affected women [5]. Furthermore, the introduction of non-invasive and highly sensitive diagnostic techniques such as magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), and computed tomography angiography (CTA) has led to a more frequent diagnosis of the disease, and, in particular, less clinically severe cases of cerebral vein thrombosis are now more commonly detected. However, venous ischemic syndromes may occur with a remarkable variability of clinical presentations and neuroimaging signs, thus representing a persisting clinical challenge. Most clinical syndromes are associated with a thrombosis of the venous sinuses; thrombosis of the cortical veins and/or deep vein thrombosis is much less common, and is more frequently detected concomitantly with sinus thrombosis.

Table 1. Clinical presentation in the two largest series of CVT patients

Ferro et al. [7]: 624 patients	%	Wasay et al. [8]: 182 patients	%
Headache	89	Headache	71
Visual loss	13	Generalized weakness	54
Papilledema	28	Focal motor or sensory deficit	36
Diplopia	13	Nausea/vomiting	35
Stupor or coma	14	Seizures	32
Aphasia	19	Walking difficulty	30
Mental status disorders	22	Drowsiness	28
Any paresis	37	Visual blurring	23
Any seizure	39	Dizziness	21
Sensory symptoms	5	Behavioral symptoms	18
Other focal cortical sign	3	Slurred speech/inability to speak	16
		Coma	15
		Fever	14

Clinical Presentations

Venous ischemic syndromes have a wide spectrum of signs and symptoms, which may evolve suddenly or over the weeks. Therefore, symptom onset can be either acute, subacute or chronic. Clinical presentation may frequently mimic many other neurological conditions such as meningitis, encephalopathy, benign intracranial hypertension, and arterial stroke. In a recent study of 239 patients who underwent extensive diagnostic work-up for suspected cerebral vein thrombosis, the disease was objectively diagnosed in 16.3% of the patients [6]. The most common clinical presentations include headache, seizures, focal neurological deficits, altered consciousness, and papilledema, which can present in isolation or in association with other symptoms. The prevalence of each clinical presentation in the two largest series of patients with cerebral vein thrombosis is presented in table 1 [7, 8]. Overall, the most frequent, but least specific clinical presentation of cerebral vein thrombosis is headache, which is present in 75–90% of adult patients [7, 8]. Headache in patients with underlying venous thrombosis typically increases gradually over a couple of days, but it can also start rapidly, mimicking a subarachnoid hemorrhage [9]. Headache has also been reported to occur more frequently in female patients than in male patients, and this observation was associated with a higher incidence of hemorrhagic lesions or infarctions at presentation [5]. According to the grouping of symptoms and signs, four main patterns have been identified: isolated intracranial hypertension, focal syndrome, cavernous sinus syndrome, and subacute encephalopathy [10]. Patients with chronic course or delayed clinical presentation may show papilledema on fundoscopy, but this finding is less common in acute cases [11]. Isolated thrombosis of the different sinuses and veins results in diverse clinical pictures. When the deep cerebral venous system is occluded, the clinical picture is usually more severe with coma, mental troubles, and bilateral motor deficits [12]. More limited thrombosis of the deep venous system can cause relatively mild symptoms [12]. In patients with parenchymal lesions, the clinical picture is also more severe. Focal or generalized seizures are more common than in other stroke types. Seizures are more typical in patients with parenchymal lesions, sagittal sinus and cortical vein thrombosis, and motor or sensory defects [13]. Coma may occur when large unilateral infarcts or hemorrhages compress

the diencephalon and brainstem. Other causes of coma are involvement of the thalamus and generalized seizures. Focal or generalized seizures followed by hemiparesis, aphasia, hemianopia, or other focal neurologic dysfunction in the absence of signs of increased intracranial pressure are associated with isolated cortical vein thrombosis [14].

Diagnosis

Although the clinical presentation is highly variable and could thus be misleading, venous ischemic syndromes should be suspected in young and middle-aged patients with recent unusual headache or with stroke-like symptoms in the absence of the usual vascular risk factors and possibly in the presence of more specific risk factors for these syndromes, in patients with intracranial hypertension, and in patients with CT evidence of hemorrhagic infarcts, especially if multiple and not confined to the arterial vascular territories. There are currently no pre-test clinical probability scores that have been validated to assist clinicians in the diagnostic approach to cerebral vein thrombosis. The use of D-dimer has been explored in small studies and the results are non-conclusive [15, 16]. CT, MRI, unenhanced time-of-flight MRA, contrast material-enhanced MRA venography, and CTA are particularly useful techniques for detecting cerebral venous and brain parenchymal changes that may be related to thrombosis. However, to achieve an accurate diagnosis, it is important to have a detailed knowledge of the normal venous anatomy and variants, the spectrum of findings (venous sinus thrombi and recanalization, parenchymal diffusion or perfusion changes or hemorrhage), other potentially relevant conditions (deep venous occlusion, isolated cortical venous thrombosis, idiopathic intracranial hypertension), and potential pitfalls in image interpretation. CT scan is commonly performed as the first-line diagnostic test. In most cases, CT scan shows indirect signs such as cerebral edema, ischemic or hemorrhagic lesions, or signs of venous stasis. Direct signs such as 'delta' or 'cord' sign can be detected in approximately one third of CT scans, whereas as many as 30% of scans can result negative [2, 17]. CTA is an important additional technique for creating images of the cerebral venous system [18]. MRI is widely used when the disease is suspected. The consequences of venous thrombosis on brain parenchyma are highly variable. With T_1- and T_2-weighted images, a localized or diffused brain swelling with normal or abnormal signals suggestive of edema, infarction, or hemorrhage is frequently observed [10]. However, MRI may be normal in up to 30% of cases. Cytotoxic or vasogenic edema may be visible using diffusion-weighted images, although, given the wide spectrum of parenchymal changes, various patterns have been reported with this technique. The most sensitive examination technique is MRI to visualize the thrombosed vessel in combination with MRA to detect the non-visualization of the same vessel [19, 20]. MRI alone is limited by flow artifacts that can lead to false positives and the absence of hyperintense signal on T_1- and T_2-weighted images at the onset of acute thrombosis. The diagnostic yield of MRA alone can be limited by the fact that, as with all other angiographic techniques, it does not differentiate between thrombosis and hypoplasia, which is extremely frequent in lateral sinuses [17].

Clinical Presentations and Neuroimaging Signs as Predictors of Outcome

The clinical outcome of venous ischemic syndromes appears to be more favorable than with arterial syndromes. The estimated mortality rate during the acute phase of the disease was estimated to be 6.3% (95% confidence interval (CI) 5.0–7.7) in a systematic review of the literature [21], with an overall mortality rate after follow-up of 9.5% (95% CI 7.9–11.1). Residual disability according to the modified Rankin scale was detected in 9.2% of the patients (95% CI 7.3–11.2) at 3–6 months, and in 9.3% of the patients (95% CI 7.6–11.0) at 12 months [21].

Clinical presentations and neuroimaging signs are important predictors of outcome following venous ischemic syndromes. Ferro and colleagues [22] reported that, among others, coma, seizure, mental status disorder, deep cerebral vein thrombosis, right intracranial hemorrhage, posterior fossa lesion, and worsening of previous focal or de novo focal deficits were independent predictors of death or dependence. Coma and intracranial hemorrhage were confirmed as predictors of poor outcome in other studies. The finding of significantly increased mortality and dependence in patients with intracranial bleeding concomitant to the ischemic syndrome is particularly relevant since up to 40% of patients with venous ischemic syndrome present with intracerebral hemorrhage [23]. Also epileptic seizures seem to be associated with an increased risk of poor outcome. Of note, in the ISCVT study, epileptic seizures resulted in being significantly more common in patients with intracerebral hemorrhage in comparison to CVT patients without intracerebral hemorrhage (55 vs. 29%; $p < 0.0001$) [23]. These findings were confirmed by Masuhr et al. [24] in a study on 194 consecutive patients with acute CVT. In this study, mortality was three times higher in patients with epileptic seizures than in patients without (36.4 vs. 12.0%).

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Spinal Cord Syndromes

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Abstract

Spinal cord infarction is much rarer than cerebral stroke, but its early recognition is important as it may signify serious aortic conditions. The most frequent type is anterior spinal artery syndrome, presenting with bilateral weakness (usually paraparesis), impairment of spinothalamic sensation and preservation of deep sensation. Depending on its level, it may present with respiratory dysfunction. More rarely, posterior infarcts sparing spinothalamic sensation but involving lemniscal sensation may be encountered. Unilateral, central or transverse infarction may also be seen probably on account of different mechanisms. Other rarer forms of spinal ischemia also include spinal TIAs, venous infarction, fibrocartilaginous embolism and decompression sickness.

Spinal cord ischemia is much rarer than brain ischemia, it was found to represent only 1% of all strokes in an autopsy series [1]. Aortic diseases are the most frequent cause [2–4]. Diagnosis can be challenging as its clinical manifestations can mimic other myelopathies (mostly inflammatory or infectious) and there is currently no test that is specific and sensitive enough to ascertain the diagnosis. Spinal MR imaging can indeed often detect an acute lesion (67–85% of the cases [3–5]), but diffusion weighted sequences are still too susceptible to artifacts to reliably confirm whether it is ischemic. The spinal vasculature is also impossible to investigate without using invasive angiographic techniques. However, prompt recognition of typical clinical pictures of spinal cord infarction can be lifesaving as they may point a life-threatening aortic disease (dissection, thrombosis or rupture of an aneurysm) that is potentially treatable if detected early.

Spinal cord infarction can be restricted in an arterial territory or be more widespread according its pathogenesis (single artery occlusion versus regional or global hypoperfusion). Spinal cord vascular anatomy is important to understand the semiology of spinal cord ischemia. The spinal cord is supplied by 3 spinal arteries running discontinuously along the spinal cord (fig. 1, left). These arteries (one anterior and two posterior) are supplied by several radicular arteries (often arising from direct aortic branches) accompanying nerve roots mostly in cervical and low thoracolumbar regions (fig. 1, right). The spinal arteries are interconnected by a thin but widespread plexus at the surface of the spinal cord. The anterior spinal artery gives unilateral alternating branches (sulcal arteries). The anterior spinal artery may be duplicated in some regions which could explain the occurrence of unilateral anterior infarction. The anterior spinal artery supplies the anterior two-thirds of the spinal cord, the remaining posterior third being supplied by the posterior arteries. We will review here the manifestations of spinal cord infarction and other rarer spinal ischemic conditions.

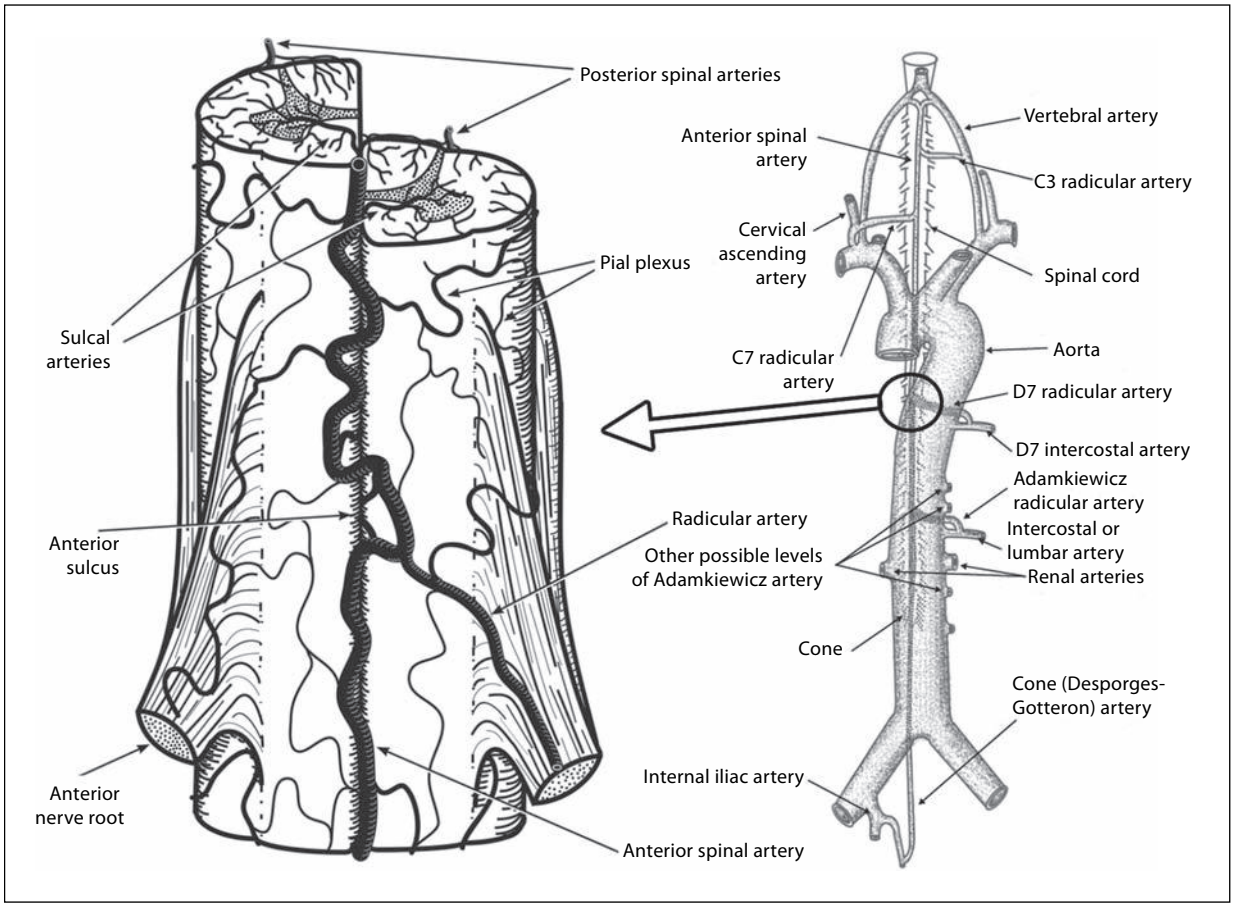

Fig. 1. Anatomy of spinal cord vascularization, aortic branches on the right and spinal cord arteries on the left. Reproduced and modified with permission of *Archives of Neurology* [3].

Spinal Cord Infarction

The different clinical syndromes are summarized in table 1. Onset of symptoms is acute, usually over a few minutes, but it may be progressive over a few hours. It is often (59–82%) [3, 4] marked by a pain in the back that is usually localized at the level of the actual cord lesion. The pain has also frequently (~80% [3, 5]) a radicular irradiation. Ischemia of local meninges, vertebral body or spinal root has been hypothesized to explain this initial pain. Patients often reported that the symptoms (pain), started during a back movement or a Valsalva maneuver [3].

Anterior spinal artery infarction is by far the commonest (also referred to as anterior spinal artery syndrome). It was initially described by Preobrashenski [6] in the setting of meningovascular syphilis. It is characterized by bilateral motor deficits (mostly paraparesis) and loss of thermoalgic sensation with sparing of proprioceptive and vibratory modalities. This dissociated sensory loss is explained by the selective involvement of spinothalamic tracts which spares the posterior columns. On testing, a small suspended sensory loss can be found above the main one. Motor deficits start usually with flaccid tone and will progressively

Table 1. Summary of the clinical features of spinal cord infarction. Reproduced with permission of *Archives of Neurology* [3]

Stroke syndrome	Feature
Anterior spinal artery infarct	Bilateral motor deficit with spinothalamic sensory deficit
Anterior unilateral infarct	Hemiparesis with contralateral spinothalamic sensory deficit
Posterior unilateral infarct	Hemiparesis with homolateral lemniscal sensory deficit
Central infarct	Bilateral spinothalamic sensory deficit without motor deficit
Posterior spinal artery infarct	Bilateral motor deficit with lemniscal sensory deficit
Transverse infarct	Bilateral motor deficit with complete sensory deficit

evolve into spasticity with the appearance of corticospinal signs. With cervical cord infarction, the motor deficit can present at times with bibrachial paresis sparing the lower limbs [3]. A focal amyotrophy may develop in the myotomes at the level of the infarct due to the involvement of the anterior horns (for example, hand intrinsic muscles in low cervical infarcts). Sphincter dysfunction is common, usually with initial urinary retention evolving into a spasmodic bladder. Patients often require bladder catheterization acutely and urinary infection is a frequent early complication. Rectal tone is usually diminished acutely, but involuntary defecation can be seen later. In high cervical infarcts, respiratory failure is common and may require intubation and ventilation. Respiratory failure can be dissociated affecting only involuntary breathing with spared voluntary function (Ondine curse) [7]. The respiratory failure should not be considered as irreversible as, in our experience, even unilateral incomplete recovery can be sufficient to allow the patient to breathe spontaneously. Long term outcome mostly depends on the severity of the initial motor deficits. The initial back pain usually subsides over a few days, but the patients are at risk of developing delayed neuropathic pain [8] (with a burning character), which can be extremely difficult to treat.

Posterior arteries infarct is much rarer. It shows marked bilateral motor involvement with sparing of the spinothalamic sensation but impairment of vibratory and proprioceptive sense. When motor deficits are moderate, incoordination through involvement of spinocerebellar tracts can be seen. Lhermitte's sign is often present as a marker of the involvement of the posterior columns. In subtle cases, testing of the discrimination of the direction of touch (the patient being asked in which direction a touching stimulus is displaced on his skin) can be a sensitive test. As in anterior spinal infarcts, sphincter dysfunction is almost invariably present.

Unilateral infarcts, whether anterior or posterior, are usually less severe and present as an incomplete Brown-Séquard syndrome sparing either lemniscal or spinothalamic sensation. Unilateral infarcts have a better recovery prognosis.

Less frequently, spinal cord infarction can occur in the central region (pencil-shaped), this region may represent a watershed area. Central infarcts present with syringomyelia-like sensory symptoms, as suspended loss of thermo-algic sensation (involvement of crossing spinothalamic fibers), and also some corticospinal signs but without prominent motor deficits. Transverse infarction may be found usually after prolonged hypoperfusion.

Other Ischemic Spinal Cord Syndromes

Transient spinal cord ischemic episodes (spinal TIAs) are rare, but they can herald the definitive infarct [2, 5]. They usually present with a fluctuating paraparesis over a few minutes to one hour, sometimes in clusters. Exceptionally, these episodes can take the form of spinal cord claudication

as originally described by Déjerine [9]. During those events that are triggered by exercise, the patient experiences lower limb weakness with corticospinal signs which both disappear with rest.

Spinal cord venous thrombosis is extremely rare. Recent cases are described after interventional procedures (mostly esophageal varices ligation or sclerotherapy [10]). It presents with a progressive painful myelopathy not restricted to a particular vascular territory. Some authors wondered if absence of valves in the epidural spinal venous plexus might favor reflux of thrombi in the spinal venous circulation.

Fibrocartilaginous embolism is a rare condition presenting with a progressive painful myelopathy often following unusually intense exercise or minor trauma. Deficits appear after a delay following the onset of the pain. In the majority of the cases reported, the outcome was very poor with death within a few days. This is however potentially a bias as this diagnosis can only be ascertained with pathology [11]. In these cases, nucleus pulposus fragments are found in spinal vessels. The mechanism of this embolism is unclear.

Decompression sickness often presents with a myelopathy whose mechanism probably includes the formation of gas bubbles in spinal cord tissue and vessels (mostly veins). This usually happens in diving when the decompression procedure is not followed, but also in aviation. Symptoms usually start during decompression or shortly after with diffuse pain, ascending sensory deficits with motor and sphincter deficits. A clear sensory level may not be found because of the diffuse nature of the condition. Recompression therapy greatly improves the prognosis with up to 80% of full recovery [12]. Patients may sometimes be left with focal lower motor neuron deficits.

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Stroke is the most common neurologic disease and the leading cause of adult disability in Western countries. The initial diagnosis of stroke is clinical and needs to be done as rapidly as possible to guarantee optimal medical and interventional therapy. The emergency stroke management depends heavily upon stroke scores to quantify the damage and to speed up the diagnosis process. Unfortunately, several important stroke syndromes are not taken into consideration in these currently used stroke scores and therefore tend to be overlooked and not treated. Compiled by leading international experts, this book provides an excellent overview on current stroke syndromes, including particularly problematic clinical pictures. Thus, together with stroke scores, the publication will lead to more thorough assessments in emergency settings.

This book is indispensable for neurologists, neurosurgeons, neuroradiologists and physicians involved in the care of stroke patients.

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