Foreword

The foreword to volumes 11 and 12 of the first series of the *Handbook of Clinical Neurology* dedicated to vascular diseases (1972) started with a famous maxim ("On a l' âge de ses artères"), emphasizing the importance of vascular diseases and their relation to the aging process. Nowadays, other pathological processes are considered as even greater threats to normal aging. Cerebrovascular diseases, however, continue to be the most common life-threatening and disabling neurological disease in the USA and in many other countries. It is therefore with great pride that we present this volume of the *Handbook of Clinical Neurology* which is one of three volumes dedicated to stroke.

These three volumes are part of the third series of the *Handbook of Clinical Neurology*, for which we have editorial responsibility. In order to provide insight into physiological and pathogenetic mechanism and a basis for new therapeutic strategies for neurological disorders, we have specifically ensured that the neurobiological aspects of the nervous system in health and disease are covered, as well as the more clinical aspects of neurological disease. During the last quarter-century, dramatic advances in the clinical and basic neurosciences have occurred, and these are emphasized in each volume of the handbook. In addition to the print form, the series is now available electronically on Elsevier's Science Direct site. This makes the handbook more accessible to readers and will also facilitate search for specific information.

The present three volumes deal with various aspects of strokes. This group of disorders is bound to acquire even greater importance with the aging of the population throughout the world. The chapters gathered in these volumes were written at the original instigation of Julien Bogousslavsky and Marc Fisher, and were under their editorial supervision. For personal reasons unrelated to this series, however, Dr. Bogousslavsky has felt compelled to withdraw his name as volume editor, but we wish to record our gratitude to both editors and to all the authors for the time and effort that they dedicated to this project. As series editors, we reviewed all the chapters and made suggestions for improvement, but we were delighted to read such scholarly and comprehensive accounts of different aspects of stroke.

We hope that these volumes will appeal to clinicians and neuroscientists alike. Until a few years ago, strokes were considered "experiments of nature" which provided enormous help in understanding the functional anatomy of the brain, but for which little could be done in terms of therapeutic intervention and prevention. Advances in our understanding of the biochemical background of strokes coupled with advances in fields as diverse as epidemiology, genetics, neuroimaging, interventional radiology, surgery, and even clinical psychology have profoundly altered our approach to stroke. In the previous series dedicated to vascular diseases, only two or three chapters dealt with therapy. In the present series, no less than 11 chapters cover therapy, including prevention and management. Significant new advances continue to occur in all aspects of stroke research, leading to new insights that demand a critical appraisal. Our goal is to provide basic researchers with the foundations for new investigations. We also intend to give clinicians a source reference to enable them to gain a thorough knowledge and understanding of the clinical features and management of the many neurological manifestations of stroke.

We are grateful to all those who contributed their time and expertise to summarize developments in their field and helped put together this outstanding volume. As always, we are especially grateful to the team at Elsevier for their unfailing and expert assistance in the development and production of this volume.

Michael J. Aminoff
François Boller
Dick F. Swaab

Preface

The *Handbook of Clinical Neurology* has been a vital and comprehensive source of information for decades, encompassing the entire gamut of knowledge related to clinical neurology and its basic science underpinning. The current revamping and expansion of this historically important resource represents a major endeavor for the series editors, volume editors, and contributors. It has been my privilege to participate in this task as the volume editor for the cerebrovascular portion of the updated series.

The field of cerebrovascular disorders has experienced a rapid expansion of many aspects of knowledge from basic mechanisms of disease to enhanced diagnostic and therapeutic capabilities. These volumes dedicated to cerebrovascular diseases were conceived with the intent of comprehensively covering all of the major aspects of neurovascular disorders managed by physicians around the world. This comprehensive effort required contributions from a large number of authors from many disciplines, leading to three volumes and several thousand pages of material. I thank the contributors for their comprehensive, insightful and illuminating chapters. Their efforts and time made the completion of these volumes related to cerebrovascular disorders possible. I also thank the staff at Elsevier for their considerable efforts related to the completion of these volumes. I thank Julien Bogousslavsky for his contributions in the design and implementation of these volumes.

The knowledge base related to the field of cerebrovascular disorders continues to expand at a rapid pace. It is my hope that the material contained within these volumes will educate those who are interested in this area and inspire some to contribute to this ongoing effort so that understanding of the pathophysiological basis of these disorders and patient care will continue to improve over the coming decades.

Marc Fisher

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Chapter 22

Topographic classification of ischemic stroke

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22.1. Introduction

Cerebral ischemia is routinely classified as global versus focal, and the neurological deficit in the latter often reflects the location of the infarct. The supply of specific cerebral areas by specific arteries is so territorially invariable that the neurologist can sometimes predict precisely which arterial branch has been affected from the clinical signs. However, a cerebrovascular lesion does not always express itself as a clearly delineated syndrome. Ischemic stroke syndrome depends not only on the artery involved, but also on several additional factors that include the collateral circulation, whether the occlusion lies proximal or distal to the circle of Willis, variations in the circle of Willis, and variations in the region supplied by a particular artery. Thus, the same syndrome may result from a lesion in different areas while a lesion in the same area may occasionally cause different syndromes in two individuals.

The development of modern neuroimaging techniques in recent decades, in particular magnetic resonance imaging (MRI), has made possible confirmation of clinical manifestations of brain lesions in larger series of patients, and even the description of features of previously unknown vascular territories. The result of these developments is the continual emergence of evidence correlating anatomical regions with functions and, as neuroimaging techniques improve, high-order physiological and psychological functions—such as attention, memory and thought—are becoming ever more anatomically delineated. In contrast to ischemic lesions, hemorrhagic stroke may involve the territory of more than one artery and is often accompanied by mass effect, causing dysfunction in adjoining structures and making clinical correlation difficult.

We have divided ischemic stroke syndromes into those caused by occlusion of the internal carotid artery (ICA) and its branches (anterior circulation), and those caused by occlusion of the vertebral and basilar arteries or their branches (posterior circulation). Since watershed infarcts may involve both circulations, these are discussed separately at the end of the chapter.

22.2. Pitfalls at clinical assessment

It is important to determine whether a lesion is in the anterior or posterior circulation, and whether it is cortical or subcortical, since management and prognoses differ markedly in these different situations. For instance, thrombolysis can be less efficacious for small subcortical infarcts than for cortical infarcts, and a wider time window for treatment may be more acceptable in catastrophic vertebrobasilar lesions than in carotid territory stroke.

Taking isolated symptoms into account may be misleading. For instance, vertigo is considered a classic manifestation of posterior circulation stroke, but it can occur after infarcts involving the vestibular cortex, which is irrigated by the middle cerebral artery (MCA) (Brandt et al., 1995; Cereda et al., 2002). Although a combination of particular symptoms (e.g., vertigo and diplopia) has a localizing value for posterior circulation strokes, diagnosis may be difficult during the very early phase. Moreover, patients with hemodynamically important obstruction of the ICA may present classic vertebrobasilar symptoms, even in the absence of atheromatosis of the posterior circulation arteries

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(Bogousslavsky and Regli, 1985). These events are probably due to hemodynamic disturbances with an intracranial carotid–vertebrobasilar steal effect. In some cases, bilateral carotid territory ischemia may mimic vertebrobasilar symptoms (Fisher and McQuillen, 1981; Sloan and Haley, 1990). Conversely, when the carotid territory is filled by the basilar artery through the posterior communicating artery (PCoA), embolization through the vertebrobasilar system may cause carotid territory ischemia (Bogousslavsky et al., 1984). In addition, a posterior cerebral artery (PCA) infarct may be misclassified as a middle cerebral artery (MCA) infarct, since it can lead to aphasia, hemianopia, and hemiparesis due to involvement of the posterior limb of the internal capsule or motor fibers in the brainstem (Hommel et al., 1990; Chambers et al., 1991). Moreover, the PCA may receive direct supply from the ICA (fetal pattern of the circle of Willis), and isolated PCA infarcts may be caused by carotid artery disease (Pessin et al., 1989). Thus, the combination of symptoms (e.g., diplopia plus vertigo in the absence of a history of carotid territory symptoms), rather than isolated information, should be considered when ascertaining the location of the lesion.

The characterization of cortical and subcortical syndromes is also difficult since, in the very acute stage, the clinical signs may evolve over time. In particular, subcortical lesions (e.g., thalamic lesions) may result in certain "cortical" signs, such as aphasia, neglect, and apraxia. Conversely, classic, small subcortical (lacunar) syndromes may be seen after cortical lesions, and are not good predictors of lesion localization in the early phase. Although brachiofacial weakness is suggestive of infarct in the cortical territory irrigated by the MCA, it may also be seen after subcortical and other lesions (de Freitas et al., 2000).

22.3. Anterior circulation

22.3.1. Anterior cerebral artery

22.3.1.1. Anatomy and vascular territory

The anterior cerebral artery (ACA) arises from the anterior clinoid portion of the ICA as it courses over the superior surface of the optic chiasm (70%) or nerves (30%) and runs rostrally, reaching the interhemispheric fissure, where it connects with the opposite ACA through the anterior communicating artery (ACoA). The ACA is divided into a segment referred to as the A1 segment, or proximal segment, between the ICA and the ACoA, and a distal segment, or post-communicating segment. A normal ACA–ACoA complex has been defined as one in which a communicating artery connects A1 segments of equal size, and both A1 segments and the ACoA are of sufficient size to allow circulation between the two carotid arteries. One ACoA is present in 60%, two in 30%, and three in 10% of cases. The recurrent branch of the ACA, first described by Heubner, is usually the largest branch of the A1 or proximal A2 segment. Heubner's artery doubles back on the parent vessel to penetrate the anterior perforated substance as a single branch or as multiple branches, supplying the anterior part of the caudate nucleus, the anterior third of the putamen, the tip of the outer segment of the globus pallidus, the anterior limb of the internal capsule, a variable degree of the uncinate fasciculus and the olfactory regions. The A1 and A2 segments, and the ACoA, give off small arterial branches to the anterior perforated substance, subfrontal area, dorsal surface of the optic chiasm, suprachiasmic area and hypothalamus (Perlmutter and Rhoton, 1976; Gomes et al., 1984). The main trunk of the ACA, the pericallosal artery or distal ACA, begins in the ACoA and runs dorsally around the genu of the corpus callosum, then continues in a sulcus between the corpus callosum and the cingulate gyrus up to the parieto-occipital fissure. The callosomarginal artery is the major branch of the pericallosal artery. It courses above the cingulate gyrus and runs into the cingulated sulcus and is absent in 18% of brains. The deep branches of the ACA arise from the proximal portion, near the circle of Willis, whereas the cortical branches, usually 11 in number, arise from the distal ACA (Fig. 22.1) (Marino, 1976; Perlmutter and Rhoton, 1978).

The ACA cortical branches supply blood to the anterior three-quarters of the medial surfaces of the

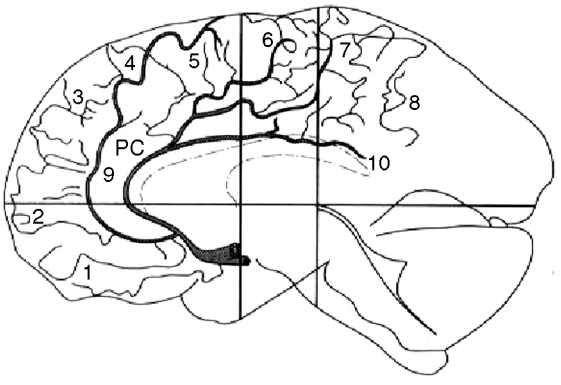

Fig. 22.1. Diagram of the main branches of the anterior cerebral artery on the medial surface of the brain. 1 = orbitofrontal; 2 = frontopolar; 3 = anterior internal frontal; 4 = middle internal frontal; 5 = posterior internal frontal; 6 = paracentral; 7 = precuneal; 8 = parieto-occipital; 9 = callosomarginal; 10 = posterior pericallosal; PC = pericallosal (Marino, 1976).

hemisphere, including the medial–orbital surface of the frontal lobe, the frontal pole, a strip of the lateral surface of the hemisphere along the superior border, and the anterior four-fifths of the corpus callosum (Fig. 22.2). The anatomy of the anterior circle of Willis is so varied that several variations of the ACA may be found. Anomalies of the distal ACA include triplication of the post-communicating segment, failure of pairing of the distal ACA, crossover of branches from one to the other hemisphere and bihemispheric branches. Particularly common are hypoplastic A1 segments, with both distal ACAs filling from the larger A1 segment. In the unpaired ACA, instead of a right and left ACA, only a single artery is present, irrigating the mesial surface of both hemispheres. When an unpaired artery or an artery with a broad bihemispheric distribution is occluded, an identical syndrome to that produced by blocking both ACA can occur (Baptista, 1963).

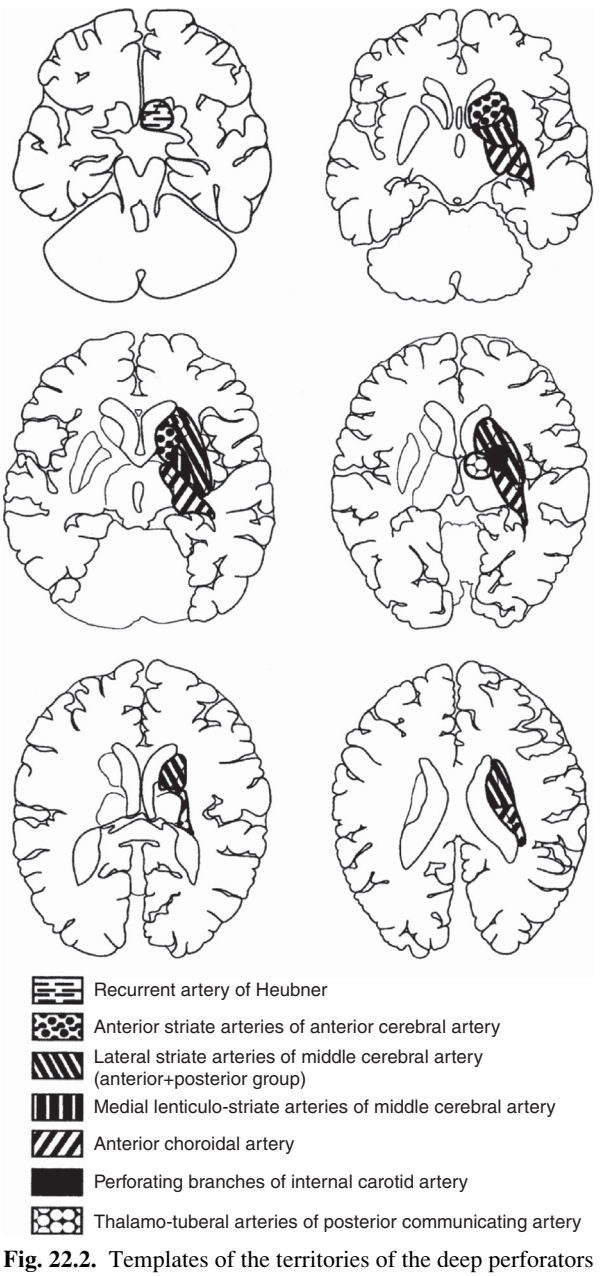

Fig. 22.2. Templates of the territories of the deep perforators in the carotid system. Reprinted from Adams, Jr 2005, with permission.

22.3.1.2. Etiology and frequency

Anterior cerebral artery infarcts (Fig. 22.3) are rare, accounting for 0.6% to 3% of acute ischemic strokes (Gacs et al., 1983; Kazui et al., 1993) (Table 22.1). Of 1,490 patients with first-ever stroke (ischemic or hemorrhagic) admitted to our center and entered into the Lausanne Stroke Registry (LSR) during its first seven years of existence, only 27 had an infarct limited to the ACA territory, as shown by computerized tomography (CT) (Bogousslavsky and Regli, 1990a). Since the ACA on one side can supply the opposite ACA through the ACoA, occlusion of one ACA stem may be asymptomatic, and this may partly explain the infrequency of infarcts in the ACA territory.

Embolism from either the carotid artery or the heart is the most common cause of ACA infarcts in Caucasians (Gacs et al., 1983; Bogousslavsky and Regli, 1990a), while in oriental populations they are mainly attributable to intracranial atherosclerosis (Kazui et al., 1993). Infarcts can also be secondary to rupture or surgery of a saccular aneurysm of the ACoA, and are commonly secondary to vasospasm after rupture of saccular aneurysms of the ACoA or the ACA. Compression of the callosomarginal artery against the falx during transfalcial herniation is another cause of ACA territory infarct (Rothfus et al., 1987). Dissections of the ACA have occurred either spontaneously or after trauma, and produce infarcts or subarachnoid hemorrhages (Amagasa et al., 1988; Ishibashi et al., 1995). Spontaneous dissections of the ACA are very rare, and middle-aged patients are most commonly affected. In patients with ischemic lesions, the lesion was most frequent in the second portion of the ACA, and in the bleeding group the characteristic finding of dissection was seen at any site of the ACA (Ohkuma et al., 2003).

22.3.1.3. Clinical features

Weakness, the most common neurological disturbance, is seen in almost all patients. The paresis classically involves mainly or only the lower limb, although faciobrachial paresis may occasionally be seen (Bogousslavsky and Regli, 1990a). Isolated facial

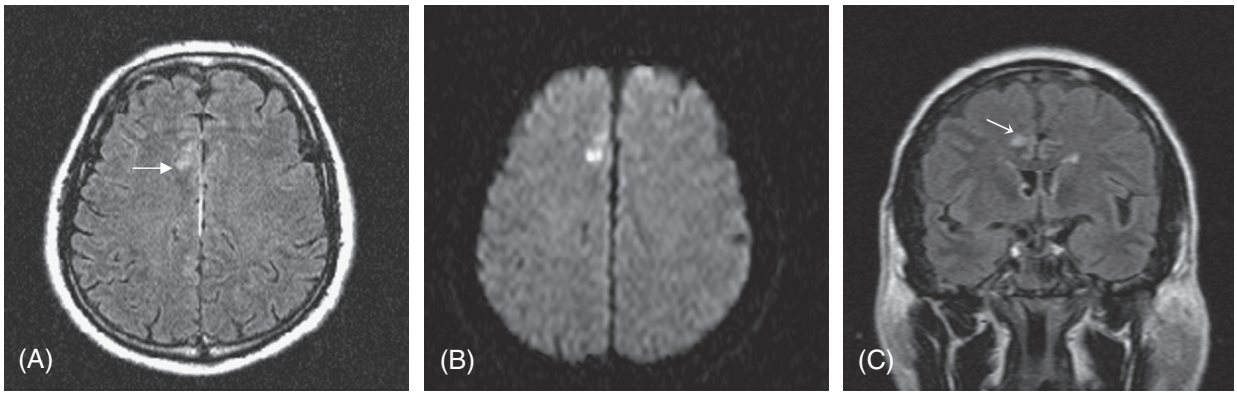

Fig. 22.3. MRI scan of a hypertensive 57-year-old man presenting with left leg weakness, showing a small infarct in the territory of the right anterior cerebral artery on FLAIR (A axial, C coronal) and diffusion weighted sequences (B).

weakness has been described after deep (caudate) infarcts (Caplan et al., 1990). Complete hemiparesis may be due to extension of the lesion into deep structures. Involvement of Heubner's artery and its supply to the anterior limb and genu of the internal capsule may be responsible for pronounced weakness of the arm and face in the presence of ACA occlusion (Critchley, 1930). Large variability in the cortical area distribution of the ACA has been demonstrated, and in such individuals an infarct would include arm and hand representations on the primary motor cortex (Van der Zwan et al., 1992). An infarct in both ACAs causes paraparesis, and is common after bilateral ACA vasospasm following ACoA aneurysm rupture (Greene et al., 1995). In thrombotic infarcts, paraparesis is especially likely to occur in the case of an anomaly of the anterior part of the circle of Willis, such as a hypoplastic A1 or an unpaired ACA (Borggreve et al., 1994).

Sensory impairments are present in about half of patients, always with hemiparesis, showing almost the same distribution (Bogousslavsky and Regli, 1990a). Depending on the extent of the ACA and collaterals from the PCA, sensory loss may be mild or absent. The contralateral grasp reflex may be present after lesions involving the orbitofrontal cortex or underlying white matter, which are in the territory of the orbitofrontal and frontopolar arteries (Kumral et al., 2002).

Urinary and fecal incontinence may be observed in patients with unilateral or bilateral infarcts, occurring in patients with large lesions involving superior and medial parts of the frontal lobes. Fecal incontinence occurs less frequently, probably due to a different physiological–anatomical basis for the urinary sphincter system (Andrew and Nathan, 1964; Kumral et al., 2002).

In terms of language, disorders of initial mutism and transcortical motor aphasia (i.e., decreased spontaneous speech, intact repetition, and good comprehension) are occasionally seen. The supplementary motor area seems to be a crucial region in the development of speech disorders (Kumral et al., 2002). Mutism may be observed after either right or left lesions. Transcortical motor aphasia is present after left lesions and its prognosis is usually good, although some patients have persistent difficulty initiating and maintaining narrative speech (Alexander and Schmitt, 1980).

Table 22.1

Arterial territories involved in 3,803 patients with first-ever ischemic stroke enrolled in the Lausanne stroke registry between 1979 and 1997

Arterial territory	*n*	%
Subcortical*	927	24.4
Anterior MCA	549	14.4
Brainstem	486	12.8
Complete MCA†	387	10.2
Posterior MCA	377	9.9
Posterior cerebral artery	231	6.1
Thalamus	186	4.9
Cerebellum	147	3.9
Multiple cortical	146	3.8
Multiple subcortical	110	2.9
Multiple VB	104	2.7
Watershed	93	2.4
Anterior cerebral artery	60	1.6
Total	3803	100.0

MCA = middle cerebral artery, VB = vertebrobasilar.
*deep infarcts in the anterior circulation (perforators of the MCA, anterior cerebral artery, and anterior choroidal artery).
†also includes concomitant MCA and anterior cerebral artery infarcts or concomitant MCA and posterior cerebral artery infarcts
From de Freitas and Bogousslavsky (2005).

Neuropsychological disturbances are common and include motor or spatial neglect, callosal disconnection syndrome, and mood disorders. Callosal disconnection syndrome, originally described after post-surgery occlusion of the left ACA (Geschwind and Kaplan, 1962), is characterized by left ideomotor apraxia (inability to execute skilled movements with the left hand) and left-hand agraphia and/or tactile anomia (inability to name objects placed in the left hand), and is relatively rare. It is speculated that, due to a callosal lesion, inputs from the right hemisphere cannot reach the areas responsible for ideomotor praxis and language in the left hemisphere, and the right hemisphere cannot function properly in isolation (Geschwind and Kaplan, 1962). A variety of mood disorders have been observed, such as acute confusion, disinhibition syndrome with euphoria and inappropriate laughing ("Witzelsucht"), and a continuum from abulia (lack of spontaneity of action and speech) with unilateral lesions, extending to akinetic mutism with bilateral lesions. Akinetic mutism refers to a state of absence of speech, voluntary movements, emotional expression, and limited responsiveness to stimuli, with integrity of primary motor and sensory functions, but with the superficial appearance of alertness, and may be caused by bilateral ACA territory infarcts (Freemon, 1971). Similar findings can be present after deep infarcts in the ACA territory involving the caudate nuclei and neighboring structures, and are attributed to interruption of cortical–subcortical circuits (Caplan et al., 1990).

Not all patients with ACA occlusion and left-sided apraxia perform well on bimanual tasks, and sometimes the hands actually seem to fight each other—alien hand syndrome. The symptoms of alien hand syndrome vary, and patients may experience movements of an extremity as involuntary and frequently contrary to the patient's stated intention. According to some authors, alien hand syndrome is actually two distinct syndromes. Frontal alien hand syndrome occurs in the dominant hand, is associated with reflexive grasping, groping, and compulsive manipulation of tools, and results from damage to the supplementary motor area, anterior cingulated gyrus, and medial prefrontal cortex of the dominant hemisphere and anterior corpus callosum. Callosal alien hand syndrome is characterized primarily by intermanual conflict and requires only an anterior callosal lesion (McNabb et al., 1988; Feinberg et al., 1992; Chan and Ross, 1997). The alien hand syndrome phenomenon is possibly related to other bizarre signs associated with callosal damage, including diagnostic dyspraxia, a peculiar dissociative behavior in which one of the patient's hands, usually the left hand of a right-handed patient, acts at cross-purposes to the other (Tanaka et al., 1990).

Involuntary movements, such as hemiparkinsonism and asterixis, have been described after ACA territory infarcts. Asterixis develops in the acute stage in patients with minimal arm weakness, whereas parkinsonism is usually observed after motor dysfunction and improves in patients with initially severe limb weakness. Asterixis is correlated with small lesions preferentially involving the prefrontal area and parkinsonism, to relatively large lesions involving the supplementary motor area or cingulated gyrus (Kim, 2001). The clinical findings after ACA infarcts are summarized in Table 22.2.

22.3.2. Anterior choroidal artery

22.3.2.1. Anatomy and vascular territory

The anterior choroidal artery (AChA) is a long, narrow artery, on average about 1 mm in diameter, usually arising from the stem of the ICA just above the origin of the PCoA, but sometimes from the bifurcation of the ICA, from the MCA, or from the PCoA (Herman

Table 22.2

Anterior cerebral artery territory infarcts: neurological features

Hemiparesis: crural predominance	
Brachiofacial (with deep extension of the infarct)	
Hemihypesthesia: same distribution as hemiparesis	
Contralateral grasp reflex	
Urinary (fecal) incontinence	
Left-sided lesions:	Initial mutism
	Transcortical motor aphasia or minor variants (Right motor neglect)
	Unilateral left apraxia
	Abulia, apathy (euphoria, disinhibition)
	"Frontal" syndrome (impaired ability to perform conflicting tasks)
Right-sided lesions:	Initial mutism
	Left motor, spatial neglect
	Abulia, apathy (euphoria, disinhibition)
	Acute confusional state
	"Frontal" syndrome
	Ipsilateral grasp reaction
Bilateral lesions:	Bilateral hemiparesis including pseudoparaplegia
	Akinetic mutism, severe mood disturbances
	Long-lasting incontinence

Parentheses indicate manifestations that are not very common.
From De Freitas and Bogousslavsky (2005).

et al., 1966; Rhoton et al., 1979). Rarely, the AChA is absent, and duplicate AChAs have been described (Carpenter et al., 1954; Hussein et al., 1988). It runs posteriorly and divides into the superficial and perforating branches. The perforating branches supply the posterior two-thirds of the posterior limb of the internal capsule, the internal segment of the globus pallidus, and part of the ventrolateral thalamus (Fig. 22.2). The superficial branches supply the optic tract and radiation, part of the lateral geniculate body, and part of the temporal lobe, where it penetrates to supply the choroid plexus and then anastomoses with the posterior choroidal artery. It is disputable whether the posterior paraventricular corona radiata is supplied by its perforating branches (Mohr et al., 1991; Hupperts et al., 1994; Hamoir et al., 2004). Branches of the AChA anastomose with those of the posterior communicating, posterior cerebral, internal carotid, middle cerebral, and lateral posterior choroidal arteries. The area supplied by the AChA therefore depends on the number of anastomoses (Carpenter et al., 1954; Helgason, 1988).

22.3.2.2. Etiology and frequency

For many years, AChA infarcts (Fig. 22.4) were considered rare. However, in one study on 100 consecutive patients with an infarct in the territory of the deep perforators from the carotid system, 23% had infarcts in the territory of the AChA (Ghika et al., 1989).

Whether AChA infarcts are caused by small-artery disease or embolism is a matter of dispute. Most AChA small infarcts are probably secondary to small-artery disease (Hupperts et al., 1994), with hypertension as the single most important risk factor (Bruno et al., 1989) while large-artery disease and cardio-embolism play an important role in large infarcts (Levy et al., 1995). Surgical ligation of the AChA has been performed to abolish the tremor of Parkinson disease (Cooper, 1954). Patients who underwent clipping for an AChA aneurysm may be at high risk of post-operative ischemia (Friedman et al., 2001).

22.3.2.3. Clinical features

First described by Foix et al. in 1925, the triad of hemiplegia, hemianesthesia, and hemianopia was considered the classic triad of AChA infarcts for some time. However, CT studies have extended the clinical spectrum of these infarcts (Bogousslavsky et al., 1986; Decroix et al., 1986; Helgason et al., 1986; Ghika et al., 1989; Levy et al., 1995). Weakness is almost always present, usually involving the face, arm, and leg. The severity of the weakness is impressive (Decroix et al., 1986), especially after large infarcts. Paradoxically, serious hemiparesis is rarely reported after AChA surgical ligation (Helgason et al., 1986c). Sensory impairment is usually incomplete and transient (Helgason et al., 1986).

Lacunar syndromes, such as pure motor syndrome, sensorimotor syndrome, and ataxic hemiparesis, are common in patients with small AChA infarcts, and were present in 67 out of 77 patients in one study (Hupperts et al., 1994). Another lacunar syndrome, hypesthesic ataxic hemiparesis, was first described after an AChA infarct (Bogousslavsky et al., 1986c). In general, the frequency of ataxic hemiparesis is not high in patients with small deep infarcts (Hupperts et al., 1994). Visual field defects are probably the most inconsistent feature of the clinical triad and, when present, are often temporary. Visual field deficits are rare in small, but common in large infarcts. They may be caused by ischemia in three different parts of the visual pathway, the optic tract, lateral geniculate body, and optic radiation (geniculocalcarine tract). The optic radiation is the structure most frequently affected and

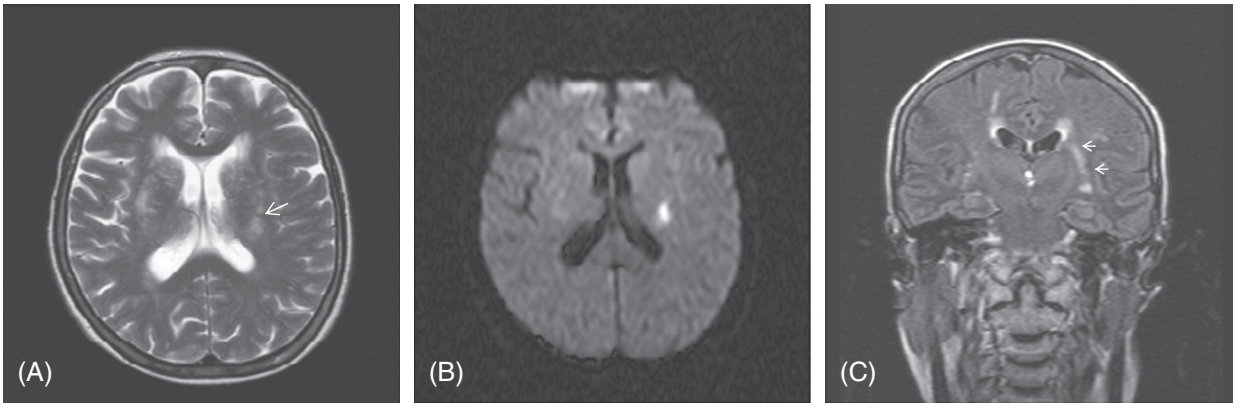

Fig. 22.4. Left anterior choroidal artery infarct shown by T2-weighted MRI (arrow) (A); diffusion-weighted MRI (B); or a coronal slice of a FLAIR sequence (arrows) (C).

leads to a congruent homonymous hemianopia with macular sparing (Decroix et al., 1986). Involvement of the lateral geniculate body causes hemianopia with sparing of a horizontal sector or superior quadrantanopia with macular sparing. Optic tract infarct should produce incongruent hemianopia without pupillary reaction to light stimuli but, in a review of described AChA infarcts (Helgason et al., 1986), this was not found to be the case. The low rates of hemianopia in AChA infarcts may be caused by the small size of most of the infarcts.

Cortical signs are not rare and are often seen after large infarcts. They include visual neglect, anosognosia (denial of illness), apraxia, motor impersistence, and eye and head deviation (Decroix et al., 1986; Helgason et al., 1986; Levy et al., 1995). In a neuropsychological study including four patients, cognitive dysfunctions were present in all four. Three patients with right-sided lesions had severe visual neglect, constructional apraxia, alexia due to disorders of visuospatial strategy, anosognosia, and motor impersistence. The patient with the left-sided lesion had mild aphasia with impaired fluency, semantic paraphasias, perseveration, and a decreased psycho-linguistic ability, but no neglect (Cambier et al., 1983). These findings may be explained by lesions in the posterior limb of the internal capsule interrupting the connections between the thalamus and cortex (Decroix et al., 1986). Pseudobulbar mutism is rarely attributed to bilateral discrete posterior limb internal capsule-medial globus pallidus infarct. Acute pseudobulbar mutism has been described in nine patients with bilateral AChA infarcts (Helgason et al., 1988).

22.3.2.4. Prognosis

There are few studies reporting prognosis in AChA infarcts. In one study, AChA infarcts had a lower 30-day case fatality and one-year mortality rate than other small deep infarcts but, because of the low number of patients, multivariate analysis could not be pursued (Hupperts et al., 1994).

22.3.3. Middle cerebral artery

22.3.3.1. Anatomy and vascular territories

The anatomy is shown in Fig. 22.5 and the blood supply in Fig. 22.6 (Gibo et al., 1981). The MCA arises from the bifurcation of the ICA at the medial end of the Sylvian fissure, just lateral to the optic chiasm. The horizontal (M1) segment generally gives rise to 5–17 small arteries (lenticulostriate branches of Duret, deep penetrators). These are classified into medial and lateral branches and penetrate into the posterior and lateral portions of the anterior

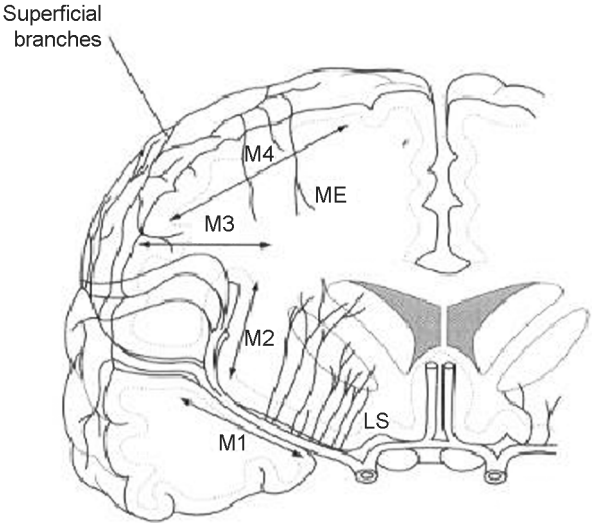

Fig. 22.5. Segments of the middle cerebral artery: M1 = sphenoidal segment; M2 = insular segment; M3 = opercular segment; M4 = cortical segment; LS = lenticulostriated arteries; ME = medullary arteries.

perforated substance. The MCA stem then often divides into two trunks (anterior or superior, and posterior or inferior) or, more rarely, into three trunks or multiple smaller divisions with no major trunk (Gibo et al., 1981). It turns 90° and runs over the insula, forming the M2 (or insular) segment, which terminates in the circular sulcus of the insula. The M3 (opercular) segment courses over the surface of the opercula and reaches the superficial part of the Sylvian fissure, where it makes two 180° turns. The branches forming the M4 (cortical) segment begin at the surface of the Sylvian fissure and extend over the cortical surface. The medullary branches arise from the superficial branches, perforate the white matter of the hemispheres, and run toward the upper part of the lateral ventricles.

The MCA cortical territory encompasses most of the lateral surface of the hemisphere, all of the insular and opercular surfaces, the lateral part of the orbital surface of the frontal lobe, the temporal lobe, and the lateral part of the inferior surface of the temporal lobe. The lenticulostriate branches of the MCA supply part of the head and body of the caudate nucleus, the upper part of the anterior limb, the genu and anterior part of the posterior limb of the internal capsule, the putamen, and the lateral pallidum (Fig. 22.2). The medullary branches of the superficial MCA system supply the centrum semiovale, which comprises the central white matter of the cerebral hemispheres, the superficial part of the corona radiata, and the long association bundles. We will describe separately the causes and clinical findings of occlusion of the MCA stem (complete

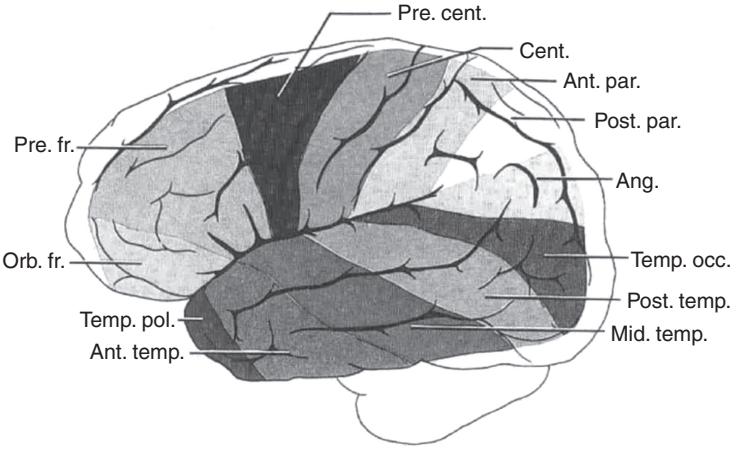

Fig. 22.6. Cortical territories of the 12 branches of the middle cerebral artery. Orb fr = orbitofrontal; Pre fr = prefrontal; Pre cent = precentral; Cent = central; Ant par = anterior parietal; Post par = posterior parietal; Ang = angular artery; Temp occ = temporo-occipital; Post temp = posterior temporal; Mid temp = middle temporal; Ant temp = anterior temporal; Temp pol = temporopolar (Gibo et al., 1981).

MCA), its superficial branches, deep perforators, and medullary branches.

22.3.3.2. Superficial (pial) and complete (deep plus superficial) middle cerebral artery infarcts

22.3.3.2.1. Etiology and frequency

Infarcts within the complete territory of the MCA and within the territory of the superficial branches of the MCA are often due to cardio-embolism or large-artery disease (Blackwood et al., 1969; Lhermitte et al., 1970; Caplan et al., 1985). Although in situ atherosclerosis of the MCA stem is considered rare, it may be much more frequent in black or oriental patients (Caplan et al., 1985). In the LSR, cardiac sources of embolism were more common in patients with infarcts in the territory of the posterior division of the MCA than in those with infarcts in the territory of the anterior division (Bogousslavsky et al., 1989). These infarcts constitute one-third (34.5%) of all ischemic infarcts in the LSR: 14.4% in the territory of the anterior division of the MCA, 9.9% in the territory of the posterior division, and 10.2% in the territory of the deep and superficial divisions (complete MCA infarct) (Table 22.1).

22.3.3.2.2. Clinical features

22.3.3.2.2.1. Complete middle cerebral artery territory infarct

These infarcts (Fig. 22.7) are very severe and are characterized by contralateral massive hemiplegia affecting the face, arm, and leg, hemianesthesia, homonymous hemianopia, and head and conjugate ocular deviation toward the infarct. Global aphasia is present in left-sided lesions, whereas hemineglect and

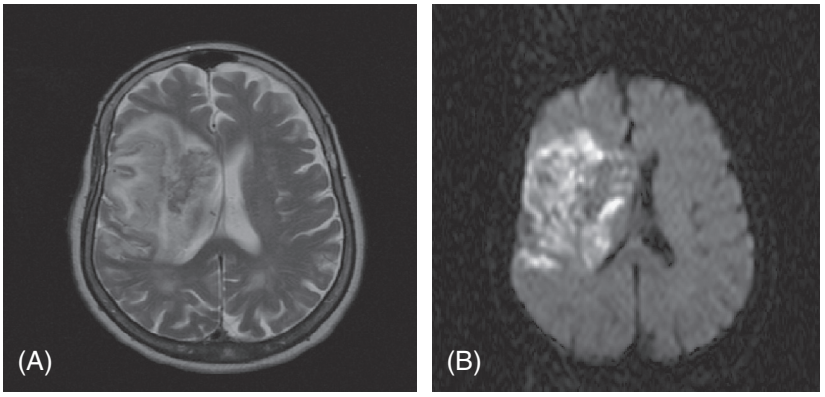

Fig. 22.7. T2 (A) and diffusion-weighted (B) MRI sequences showing an infarct involving almost all the territory of the middle cerebral artery; part of the inferior (posterior) division is spared.

Table 22.3

"Peripheral" vegetative changes after large hemispheric infarcts

Acute	Ipsilateral	Thermoregulatory hemihypohydrosis
		Central Horner syndrome (telodiencephalic ischemic syndrome)
	Contralateral	Hyperhydrosis
		Decrease in skin temperature (cold stroke syndrome)
Chronic	Contralateral	Painful trophic changes
		Muscle denervation

From de Freitas and Bogousslavsky (2005).

visuospatial impairment are seen with right-sided lesions. "Peripheral" vegetative changes are likely to develop in this type of large cerebral infarct, but are commonly overlooked (Table 22.3). Patients may initially be alert but, from the first to the fourth day after stroke, impairment of consciousness develops due to cerebral edema. Impairment of consciousness may be present from the beginning and, in the experience of one of the present authors (Bogousslavsky), is the best predictor of death (Heinsius et al., 1998). The prognosis is very poor, with only 10% of patients independent at 1 year (Bamford et al., 1991). Mortality is also high, but the death rate varies from 22% to 78%, probably due to different selection criteria (Hacke et al., 1996; Heinsius et al., 1998).

22.3.3.2.2.2. Superficial (pial) middle cerebral artery territory infarct

Involvement of all of the anterior and posterior superficial branches, with sparing of the deep territories, is rare. The clinical findings are similar to those of complete MCA infarcts, with contralateral homonymous hemianopia and head and conjugate eye deviation toward the lesion often being present, but motor and sensory impairments usually spare the leg. The prognosis is not as bad as for complete MCA infarcts, and the higher level of consciousness allows observation of various neuropsychological findings. Left-side lesions are characterized by global or Broca's aphasia (poor and reduced speech, agrammatism, and moderate comprehension deficits), and ideomotor apraxia. Several behavior abnormalities may be seen after right-sided infarcts; these include anosognosia, left spatial neglect, motor impersistence, dressing and constructional apraxia, extinction on double-simultaneous stimulation, acute confusion, and prosopoagnosia (inability to recognize familiar faces) (Hier et al., 1983). Motor impersistence is closely correlated with anosognosia and more severe hemiplegia, and is often seen after large lesions. Aprosodia, which refers to monotonous speech without melodic and emotional inflections, is rare.

22.3.3.2.2.3. Anterior pial middle cerebral artery territory infarct

The neurological picture includes faciobrachial paresis and sensory loss and conjugate eye deviation toward the lesion (Foix and Levy, 1927; Derouesné, 1973). Hemianopia is very rare. After left-sided infarcts, Broca's aphasia may be observed from the beginning or a few days after initial mutism (aphemia). Depression is often reported after left frontal infarcts. Aprosodia and anosognosia may be seen with right-sided infarcts.

22.3.3.2.2.4. Infarcts in the territory of branches of the anterior pial MCA

The territory supplied by each artery and the clinical picture observed after isolated lesions are summarized in Table 22.4.

22.3.3.2.2.5. Posterior pial middle cerebral artery territory infarct

When infarcts in this territory (Fig. 22.8) cause weakness, it is slight and mainly present in the face and arm. Similarly, sensory impairment, when present, is mild and often accompanied by contralateral extinction on double-simultaneous stimulation. Contralateral homonymous hemianopia or upper quadrantanopia is found in almost all patients. Wernicke's aphasia is usually seen after left-sided infarcts and is identified by fluent speech, impaired repetition and comprehension, and phonemic and verbal paraphasias, sometimes with jargon paraphasia and acute agitation. Conduction aphasia may be observed initially or, more often, as an evolution of Wernicke's aphasia. It is characterized by fluent speech with word search and good comprehension, contrasting with impaired repetition. Right-side infarcts promote a series of neuropsychological disturbances, the most common being left spatial neglect, constructional apraxia, extinction on double-simultaneous stimulation, and severe agitated delirium (Caplan et al., 1986).

22.3.3.2.2.6. Infarcts in the territory of the branches of the posterior pial middle cerebral artery

These are summarized in Table 22.5.

22.3.3.3. Deep MCA infarcts

These infarcts are due to involvement of the lenticulostriate arteries of the MCA. They can be divided into two groups, small deep or large deep infarcts, with different causes, prevalence, clinical findings, and prognoses.

Table 22.4

Clinical findings in isolated infarcts in branches of the anterior middle cerebral artery

Artery	Territory	Clinical findings
Orbitofrontal	Orbital portion of the middle and inferior frontal gyri and the inferior part of the frontal lobe	"Prefrontal syndrome of Luria": loss of programming abilities, utilization and imitation behaviors, grasp reflex, perseverations, apathy, abulia
Precentral	Anterior and middle parts of the precentral gyrus, posterior middle frontal gyrus, and superior orbital part of the frontal lobe	Proximal brachial paresis, "premotor syndrome of Luria": inability to perform successive motor sequences smoothly, motor impersistence Left-sided lesions: transcortical motor aphasia
Central sulcus	Posterior precentral sulcus and anterior half of the post-central gyrus	Faciobrachial paresis and sensory loss, or isolated arm and hand weakness with mild sensory loss. Rarely, isolated cheiro-oral sensory loss (posterior operculum syndrome of Bruyn) Left-sided lesions: mild Broca's aphasia Bilateral: pseudobulbar palsy (Foix–Chavany–Marie syndrome)
Anterior parietal	Posterior post-central gyrus, parasagittal part of the central sulcus, anterior part of the inferior parietal gyrus, supramarginal gyrus, parts of the upper and middle temporal gyrus	Pseudothalamic syndrome of Foix–Roussy: faciobrachiocrural sensory loss mainly in the upper limb, associated with neuropsychological dysfunction. Rarely, opercular cheiro-oral syndrome Left-sided lesions: conduction aphasia, ideomotor apraxia Right-sided lesions: hemisensory and spatial neglect

From Neau and Bogousslavsky (1998).

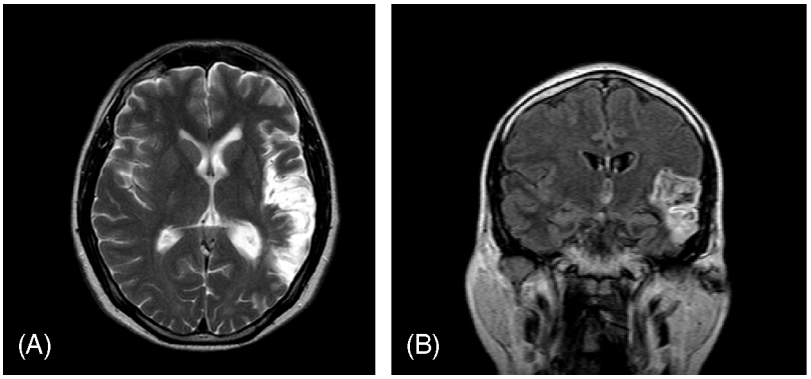

Fig. 22.8. MRI scan of a 42-year-old patient with no known risk factors for stroke presenting with Wernicke's aphasia and mild right hemiparesis and hemihypoesthesia, involving predominantly the face and arm (A). Note the involvement of the lateral part of the temporal lobe on the coronal sequence (B).

22.3.3.3.1. Small deep infarcts, or lacunar infarcts

These are secondary to involvement of the territory of only one MCA lenticulostriate artery, and are caused by lipohyalinosis, a process linked to hypertension. Atheromatosis and embolic occlusion of small vessels may also play a role (Fisher, 1982). Large-artery disease and cardio-embolism are other potential causes of these infarcts. On CT or MRI, they appear as lesions smaller than 1.5 cm, known (together with deep small infarcts of other artery territories) as "lacunes." Taken

Table 22.5

Clinical findings in isolated infarcts in branches of the posterior middle cerebral artery

Artery	Territory	Clinical findings
Posterior parietal	Posterior parts of the superior and inferior parietal lobules, including the supramarginal gyrus	Cortical sensory syndrome: astereognosia, agraphestesia, loss of proprioception. Left-sided lesions: Wernicke's aphasia; Gerstmann's syndrome (right-left disorientation, finger agnosia, acalculia, agraphia); anomic aphasia. Right-sided lesions: extinction, spatial neglect.
Angular	Posterior portions of the superior and inferior parietal lobules, inferior portion of the lateral occipital gyrus, and variable portions of the supramarginal and angular gyri	Contralateral hemianopia or lower quadrantanopia, transient weakness Left-sided lesions: isolated Gerstmann's syndrome, or accompanied by Wernicke's aphasia, transcortical sensory aphasia or anomic aphasia Right-sided lesions: extinction, spatial neglect, asomatognosia, constructional apraxia Bilateral: Balint's syndrome (psychic gaze paralysis, optic ataxia, visual inattention)
Temporal (five temporal arteries: temporo-occipital, posterior temporal, middle temporal, anterior temporal, temporopolar)	Inferior part of the lateral occipital gyrus, superior, middle and inferior temporal gyri	Contralateral hemianopia or superior quadrantanopia, transient weakness and sensory loss Left-sided lesions: isolated Wernicke's aphasia, or accompanied by right hemianopia Right-sided lesions: extinction, spatial neglect, constructional apraxia, agitated confusional state Bilateral: pure word deafness, cortical deafness

From Neau and Bogousslavsky (1998).

together, deep infarcts in the territory of the MCA, ACA, and AChoA account for one-quarter of all ischemic strokes (Table 22.1).

The clinical findings may be stereotypical and are therefore called "lacunar syndromes." Although more than 70 syndromes related to lacunar infarcts have been reported, most are minor variants of one another (Fisher, 1991). Classic lacunar syndromes include pure motor hemiplegia (involving the face, arm, and leg), pure sensory stroke, sensorimotor stroke, ataxic-hemiparesis, and dysarthria-clumsy hand syndrome. The lacunar syndrome most commonly observed in the MCA territory is pure motor hemiplegia. Infarcts restricted to the genu of the internal capsule may involve corticopontine fibers and produce a special clinical pattern of severe contralateral facial and lingual hemiparesis with dysarthria ("upper capsular genu syndrome") (Bogousslavsky and Regli, 1990b). Involvement of thalamofrontal connections has been proposed to explain an acute, confusional state with fluctuating alertness also seen after small lesions of the genu of the internal capsule ("lower capsular genu syndrome") (Tatemichi et al., 1992). Movement disorders may occasionally be seen after lacunes in the MCA territory (Fisher, 1982).

Patients with lacunar infarct often have a good prognosis. The fatality rate of lacunar infarct is low (about 1% at one month) and death is generally not due to direct neurological sequelae of the infarct (Bamford et al., 1987). Patients presenting with certain classic lacunar syndromes, such as pure motor hemiparesis and pure sensory syndrome, have a better prognosis than those presenting with sensorimotor stroke (Bamford et al., 1987).

22.3.3.3.2. Large deep infarcts or striatocapsular infarcts

These are often caused by cardio-embolism or large-artery disease. Occlusion of the MCA trunk leads to an infarct in the territory of all lenticulostriate arteries, while adequate collateral flow to the overlying cortex via transcortical and transdural anastomoses explains the cortical sparing. These infarcts typically appear on CT or MRI as a comma-shaped lesion greater than 3 cm (Fig. 22.9). They are rather uncommon, accounting for 1–6% of all strokes (Donnan et al., 1991; Boiten and Lodder, 1992).

The most common clinical presentation is that of hemiparesis and hemisensory loss with accompanying cortical features. Weakness affects mainly the upper limb. Cortical findings, such as aphasia, apraxia, and neglect, are present in more than two-thirds of patients (Donnan et al., 1991).

The prognosis of patients with striatocapsular infarcts appears to be intermediate between the good prognosis of lacunar infarct and the poor prognosis of cortical/subcortical infarct (Donnan et al., 1991). In one series, two-thirds of patients experienced at least functional recovery and half of these were able to return to work (Donnan et al., 1991). Predictors of good outcome were younger age, absence of cortical signs at presentation, and no hemodynamically significant disease on cerebral angiography.

22.3.3.4. Centrum ovale infarcts

These are caused by involvement of the medullary branches. In the LSR, an infarct restricted to the white matter territory of the centrum ovale was found in 1.6% of patients admitted for first-ever stroke (Bogousslavsky and Regli, 1992). As with deep subcortical infarcts, these infarcts can be divided into two groups, small and large.

22.3.3.4.1. Small centrum ovale infarcts

These are the most common type of stroke limited to the centrum ovale (72%). They are round or ovoid and their maximal diameter is less than 1.5 cm (Fig. 22.10). With small infarcts, chronic hypertension and diabetes are frequent, but carotid disease is rare (Bogousslavsky and Regli, 1992). These findings suggest that small centrum ovale infarcts are related to small-vessel disease involving the medullary branches in the same way as lacunar infarct is caused by disease involving the deep perforators of the MCA.

The neurological deficit, consisting of faciobrachiocrural or partial hemiparesis, sensorimotor stroke, and ataxic hemiparesis, is compatible with lacunar syndromes. Small infarcts in the centrum ovale are frequently clinically silent and are detected accidentally (Leys et al., 1994).

22.3.3.4.2. Large centrum ovale infarcts

This type of infarct involves the territory of more than one medullary branch. They have a maximal diameter greater than 1.5 cm, an irregular shape, and the geographical margins follow the inner border of the cortex. The mechanisms of large infarcts are not clear.

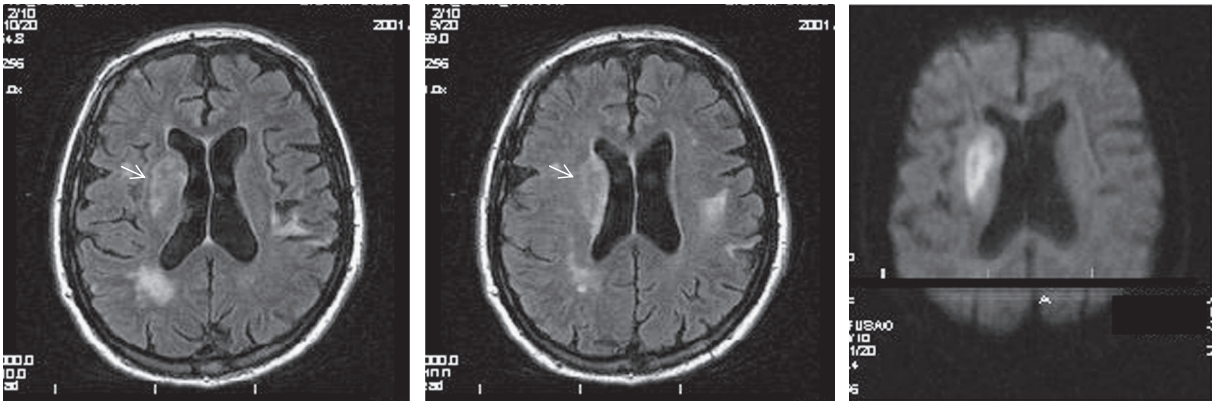

Fig. 22.9. T2 (A, B) and diffusion-weighted (C) MRI sequences showing a "comma shaped" infarct involving the territory of the lenticulostriated arteries (arrows).

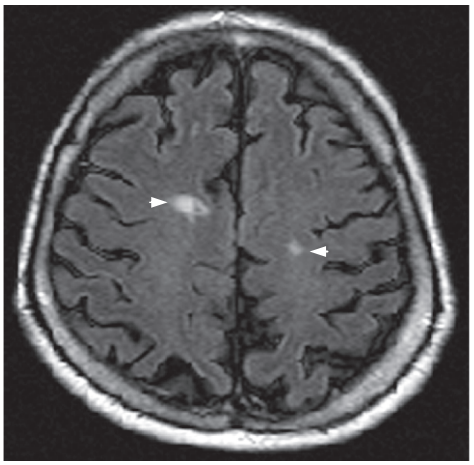

Fig. 22.10. Bilateral small centrum ovale infarcts on an MRI scan (arrowheads).

Ipsilateral carotid occlusion of greater than 50% stenosis is common (80%), which may suggest distal hemodynamic failure (Bogousslavsky and Regli, 1992). However, artery-to-artery embolism or cardiac embolism cannot be formally excluded in many instances.

The neurological signs are similar to those found in large superficial or extended MCA infarcts. The deficits are characterized by marked hemiparesis affecting the upper limb and face more than the lower extremities, with an accompanying sensory deficit, which follows a similar pattern of faciobrachial predominance. Additional elements include aphasia (dominant hemisphere infarct) or visuospatial disturbances (non-dominant hemisphere involvement).

22.4. Posterior circulation

22.4.1. Posterior cerebral artery

22.4.1.1. Anatomy and vascular territories

The anatomy is shown in Fig. 22.11 (Krayenbuhl and Yasargil, 1982). The PCAs arise from the basilar bifurcation in the pontomesencephalic junction. They course around the midbrain, anastomose with the PCoAs, and divide into cortical branches as they reach the dorsal surface of the midbrain. In about one-quarter of patients, one of the PCAs arises from the ICA; this is known as a fetal-type PCA. Studies using cerebral angiograms have shown that in 11% of hemispheres the PCA is exclusively supplied by the ICA, while in 46% the PCA was filled from both the ICA and the vertebral arteries (VA), indicating an open collateral system from the ICA via the PCoA to the PCA. Both of these configurations make it possible for emboli from the carotid to reach the PCA (Jongen et al., 2002). A useful way to designate the PCA segments is to divide the artery into the precommunal segment or P1 segment, which extends from the

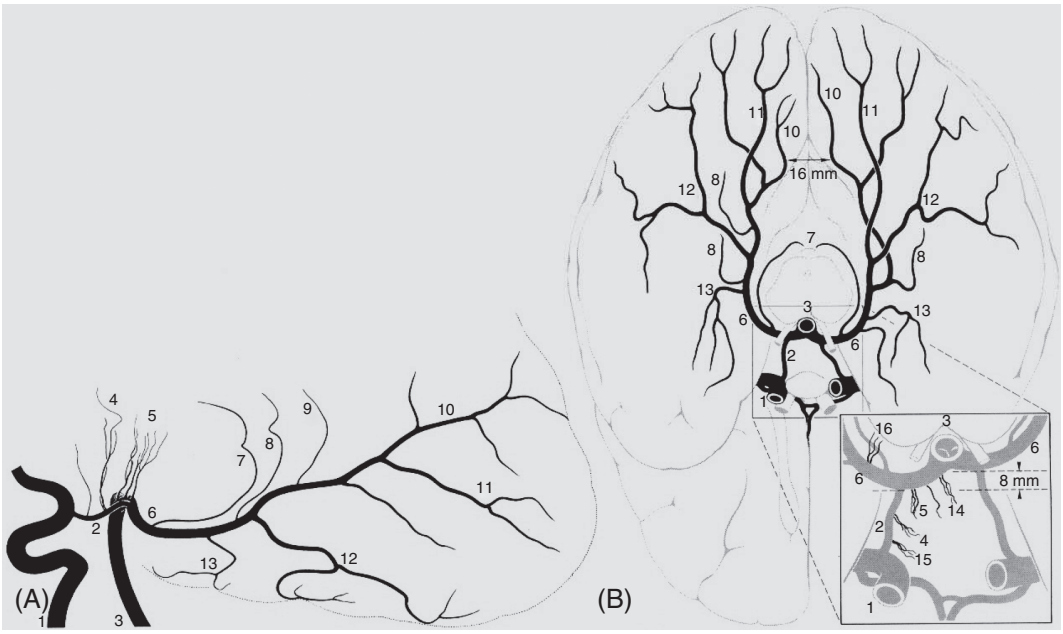

Fig. 22.11. Anatomy of the posterior cerebral artery. 1 = internal carotid artery; 2 = posterior communicating artery; 3 = basilar artery; 4 = anterior thalamoperforate arteries; 5 = posterior thalamoperforate arteries; 6 = posterior cerebral artery; 7 = medial posterior choroidal artery; 8 = lateral posterior choroidal arteries; 9 = posterior pericallosal artery; 10 = parieto-occipital artery; 11 = calcarine artery; 12 = occipitotemporal artery; 13 = anterior temporal ramus; 14 = paramedian arteries; 15 = quadrigeminal and geniculate branches; 16 = perforating peduncular arteries (Krayenbuhl and Yasargil, 1982).

bifurcation to the origin of the PCoA, and the post-communal segment, from the origin of the PCoA to the division into cortical branches. The precommunal segment gives rise to the interpeduncular arteries, paramedian mesencephalic arteries (also called thalamoperforate arteries), and the medial posterior choroidal arteries, which supply the most median part of the midbrain and thalamus (Fig. 22.12). The thalamoperforating artery consists of one or more arteries usually originating at the central segment of P1. This artery has been described as unilaterally aplastic and is sometimes even absent. When it does occur, contralateral thalamoperforator branches conduct a bilateral supply. The thalamoperforating arteries enter the posterior perforated substance and supply the anterior and part of the posterior thalamus, the posterior limb of the internal capsule, the hypothalamus, the subthalamus, substantia nigra, the red nucleus, and portions of the deep, rostral mesencephalon (Yasargil, 1984). From the post-communal segment arise the inferolateral artery (or thalamogeniculate artery) and the lateral posterior choroidal artery, which follows the curve of

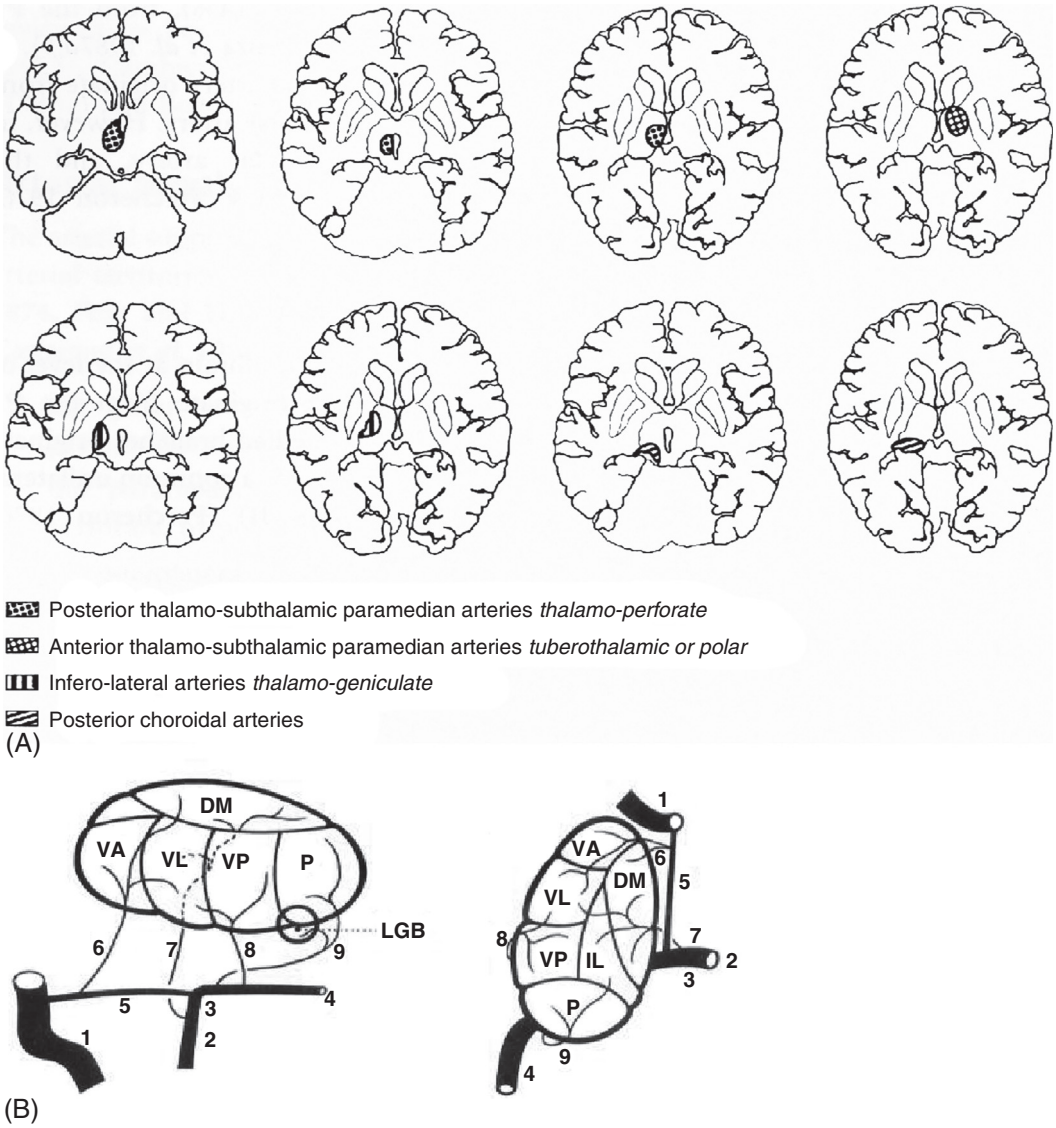

Fig. 22.12. Arterial supply to the thalamus: arterial branches (A) and template of territories (B). Arterial branches: 1 = internal carotid artery; 2 = basilar artery; 3 = posterior cerebral artery P1 (or mesencephalic artery); 4 = posterior cerebral artery; 5 = posterior communicating artery; 6 = tuberothalamic (or polar) artery group; 7 = thalamoperforate (or paramedian) artery group; 8 = thalamogeniculate (or inferolateral) artery group; 9 = posterior choroidal arteries; LGB = lateral geniculate body; DM = dorsomedial nucleus; VA = ventral anterior nucleus; VL = ventral lateral nucleus; VP = ventral posterior nucleus; P = pulvinar; IL = intralaminar nuclei (Bogousslavsky et al., 1988b).

the pulvinar and supplies it only superficially, irrigates the lateral geniculate body and a small portion of the medial temporal pole, and then enters the choroidal fissure to supply the choroid plexus of the lateral ventricle, while terminal branches anastomose with the AChA. The polar region of the thalamus is supplied by the tuberothalamic (polar) artery, which usually originates from the anterior circulation and arises from the PCoA. The cortical branches include the posterior temporal artery, parieto-occipital artery, and calcarine arteries, which supply the inferomedial part of the temporal lobe and the medial occipital lobe, including the cuneus, precuneus, and visual areas 17, 18, and 19.

For practical purposes, we will consider separately those clinical findings due to distal occlusions involving the hemispheral PCA territory and those due to proximal occlusions causing thalamic and midbrain infarcts. Infarcts involving both the proximal and distal territories are also seen, but are very rare. Midbrain infarcts due to proximal occlusions are discussed in another section of this chapter.

22.4.1.2. Cortical PCA infarcts

22.4.1.2.1. Etiology and frequency

The frequency of all PCA infarcts is about 10% (Table 22.1), and most of these involve the cortical PCA territory (Brandt et al., 2000) (Fig. 22.13). Most cortical PCA infarcts (about 70%) are caused by an embolic mechanism, mainly cardio-embolism and intra-arterial embolism (Caplan, 1996). As with MCA infarcts, PCA stenosis is not common, causing about 10% of infarcts (Castaigne et al., 1973; Pessin et al., 1987). Although Fisher (1986) considered the PCA as "the artery of migraine par excellence," the significance of migraine in PCA infarcts is controversial (Brandt et al., 2000; Steinke et al., 1997). A study of cerebral angiograms showed that, in 11% of hemispheres, there was exclusive filling of the PCA from the internal carotid artery (fetal-type) (Jongen et al., 2002). However, in a series of PCA infarcts, ICA occlusion was a rare (1–3%) cause of infarcts of the PCA (Steinke et al., 1997; Cals et al., 2002). In most cortical PCA infarcts there is calcarine branch territory involvement (86%), but some patients may exhibit a co-existence of parieto-occipital and temporal branches territories (13%) or only parieto-occipital branch territory involvement (14%) (Kumral et al., 2004).

22.4.1.2.2. Clinical features

Almost all patients (90–97%) have initial visual symptoms and are usually aware of visual loss, complaining of loss on one side of the visual space. Hallucinations in the lost visual field may be present and may be common when routinely investigated (Milandre et al., 1994). In addition, visual signs are found in more than 80% of patients and, in about half, visual field defects may be the only neurological sign (Cals et al., 2002). In a series of 117 patients, homonymous hemianopia was the most common visual deficit (67%), (macular sparing occurring in 11%), followed by quadrantanopia (22%, upper 17%, lower 5%) and bilateral deficit (4%) (Cals et al., 2002). Cortical blindness was observed in 4% of patients. Homonymous scotoma has also been seen. Sometimes, hemichromatopsia, which refers to an inability to identify colors within the field, is the only visual defect. Total absence of color perception (achromatopsia) appears to be rare (Heywood et al., 1987). Occasionally, patients may

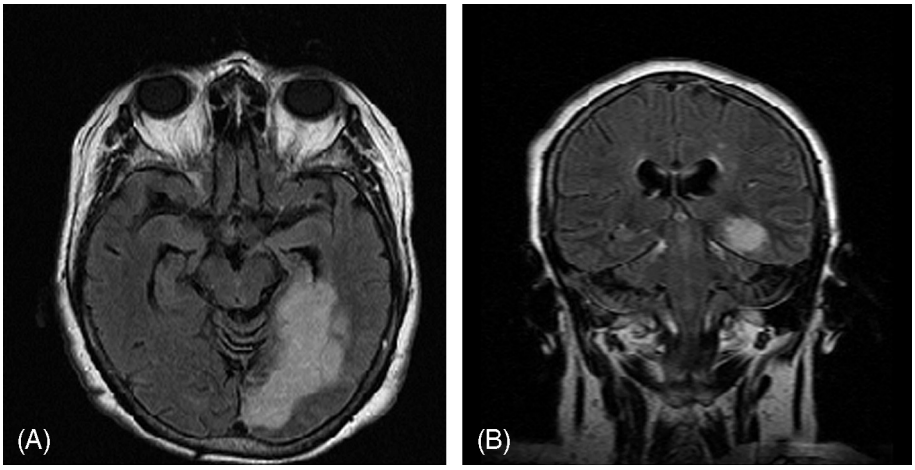

Fig. 22.13. MRI scan (A, B) showing a cortical left-sided posterior cerebral artery territory infarct. Note the involvement of the medial part of the temporal lobe on the coronal sequence (B), in contrast to Fig. 22.8.

detect motion and the presence of an object but may be unable to tell the nature of the object. Visual perseverations (palinopsia) are not common, but are specific for occipital infarcts. This syndrome usually occurs in a patient who has an impaired visual field but is not entirely blind. Hallucinations and illusions of visual movement are common in palinopsia. It is unknown whether palinopsia represents a form of seizure (Meadows and Munro, 1977; Michel and Troost, 1980).

Headache, present in about half of patients, suggests PCA infarct. About 40% of patients have sensory findings, most often in the face and hands, and these are attributed to involvement of the thalamus or adjacent white matter pathways (Georgiadis et al., 1999). Hemiparesis, mostly transient and slight, is present in about a quarter of patients (Table 22.6).

A variety of neuropsychological abnormalities may be seen, with the most common including memory impairment, language disturbances (mainly transcortical sensory aphasia and amnestic aphasia), and visual neglect. Transcortical sensory aphasia is an uncommon disturbance featuring fluent speech, with numerous paraphasias. Oral comprehension and written comprehension are impaired, but repetition is remarkably preserved with a tendency to echolalia, while denomination is also always impaired. In a restrospective study of 76 patients with cortical PCA territory infarcts, three met the criteria for transcortical sensory aphasia, with infarct only in the PCA territory. All showed involvement of the ventromedial temporal lobe, calcarine cortex and thalamus of the dominant hemisphere. Five other patients with anomia but preserved speech content and comprehension (amnestic aphasia) had similar lesions but without the involvement of the thalamus (Servan et al., 1995).

After left-sided infarcts, an inability to read, but no other basic language abnormalities (so-called "alexia without agraphia" or "pure alexia"), may be observed and is considered to be specific to PCA infarct. It is considered a disconnection syndrome, with involvement of the corpus callosum as it impedes the stimulus from the right occipital lobe from arriving at the left angular gyrus (Geschwind, 1965). Alexia with agraphia also occurs after left-sided PCA infarcts, but can also be seen after posterior MCA lesions. Verbal dyslexia is a less severe impairment in which individual letter naming is preserved. The patient cannot read whole words but adopts a strategy of recognizing

Table 22.6

Cortical posterior cerebral artery territory infarcts: neurological features

Structure involved	Neurological dysfunction
Medial temporal lobe	Memory disturbances
Occipital lobe	Lateral hemianopia or other homonymous lateral visual field cut
	Visual hallucinations, metamorphosias, monocular diplopia
	Impairment of movement perception, astereotopsis left tactile-visual anomia/left hand diagnostic apraxia (posterior callosal involvement)
	Left-sided lesion: dysmnesia (for verbal material), transient global amnesia
	Pure alexia, optic aphasia (visual anomia)
	Transcortical sensory aphasia
	Hemiachromatopsia, color anomia
	Visual hemineglect
	Acute confusional state, acute delirium
	Right-sided lesion: dysmnesia (for nonverbal material), transient global amnesia
	Visual hemineglect
	Palinopia
	Prosopoagnosia (disputable)
	Impaired mental imagery (Charcot–Wilebrandt syndrome)
	Bilateral: bilateral hemianopia, sometimes with tubular vision
	Cortical blindness, Anton's syndrome
	Balint's syndrome
	Altitudinal hemianopia
	Prosopoagnosia, visual object agnosia
	Klüver–Bucy syndrome
	Amnesia

From de Freitas and Bogousslavsky (2005).

words by naming the letters one by one. Conduction aphasia and color anomia are occasionally seen. Visual agnosia (inability to name objects shown visually) may be seen after large, left-sided lesions. Some patients may have agnosia restricted to colors. Verbal memory and learning disturbances are often observed after temporomesial involvement (Von Cramon et al., 1988). Confusional states may follow left-sided lesions (Devinsky et al., 1988), but have also been observed after right-sided lesions (Milandre et al., 1994). Fewer abnormalities are noted following right-sided lesions, but visual neglect, visual amnesia, constructional apraxia, and disorientation to place may be found.

Patients with bilateral lesions may have cortical blindness with anosognosia (Anton's syndrome). Agitated delirium and severe amnesia may accompany the syndrome. Balint's syndrome, consisting of simultagnosia (inability to see a full scene at one time), optic ataxia (abnormal hand–eye coordination), and ocular apraxia (inability to accurately fix on an object), results from bilateral occipital infarcts with lesions above the calcarine fissure. Prosopoagnosia (inability to recognize faces) is observed after bilateral lesions under the calcarine fissure. Cerebral achromatopsia, or the loss of color perception following bilateral cerebral lesions, may occur rarely.

PCA infarcts may mimic MCA infarcts in up to one-fifth of cases. The clinical syndrome of acute hemiparesis, hemisensory loss, hemianopia, visuospatial neglect, and aphasia is generally attributed to infarcts of the MCA; the same clinical features, however, can be present in PCA strokes. The PCA territory most commonly involved is the superficial PCA territory, followed by the proximal PCA territory (Chambers et al., 1991; Maulaz et al., 2005).

22.4.1.2.3. Prognosis

While patients with superficial PCA territory infarct generally have good outcomes, there is a risk of death for those with additional midbrain involvement. These patients have poorer functional outcomes, as their motor deficits are severe and persistent (Brandt et al., 2000). In one study, 7% of patients died in the acute stroke phase, all of them having infarcts in the deep PCA territory (Milandre et al., 1994). Visual and neuropsychological disturbances comprise the most frequent and important long-term disabilities.

22.4.1.3. Thalamic infarcts

22.4.1.3.1. Etiology and frequency

Infarcts restricted to the thalamus account for 11% of vertebrobasilar infarcts (Bogousslavsky et al., 1988c). In a study carried out at our center, the main cause of thalamic infarcts was found to be small artery disease (14/40), followed by large artery atheroma (7/40), cardio-embolism (5/40), and migraine stroke (4/40) (Bogousslavsky et al., 1988b). Except in the case of bilateral paramedian infarcts, which are highly suggestive of cardio-embolism, involvement of one of the main arterial territories of the thalamus was not associated with a particular cause of stroke. Clinicoradiological–anatomical studies suggest that it is appropriate to divide thalamic infarcts into four groups based on the four main arterial territories. Inferolateral infarcts are the most common (45%), followed by paramedian (35%), polar (12.5%), and posterior choroidal (7.5%) infarcts (Bogousslavsky et al., 1988b). Only one of 40 patients in one study of thalamic infarcts died in the acute phase, and the annual death or stroke risk was 7.4% (Bogousslavsky et al., 1988b). Late disability in survivors was related to neuropsychological sequelae and, more rarely, to persistent pain.

22.4.1.3.2. Clinical features

22.4.1.3.2.1. Inferolateral infarcts

The inferolateral or thalamogeniculate territory is supplied by the thalamogeniculate arteries, which originate at the second part of the PCA. This territory includes the ventrolateral nucleus, ventroposterior nuclei (ventroposterolateral, ventroposteroinferior, and ventroposteromedian nuclei), and ventromedian nuclei. The ventrolateral nucleus has connections to the cerebellum and the motor and prefrontal cortex. The ventroposterolateral nucleus receives inputs from the medial lemniscal and spinothalamic pathways, whereas the ventroposteromedial nucleus receives inputs from the trigeminothalamic pathway (Schmahmann, 2003; Carrera and Bogousslavsky, 2006).

Pure sensory stroke is the most common manifestation. The hemisensory deficit may involve the entire hemibody, but may also be partial, with cheiro-oral, cheiro-podo-oral, or pseudo-radicular patterns. In their initial report, Dejérine and Roussy (Dejérine and Roussy, 1906) indicated that delayed (weeks to months) pain may develop ("anesthésie douloureuse").

In a few instances, the infarct can involve the adjacent portion of the internal capsule, with corresponding hemiparesis associated with sensory loss. Hemiataxia is not uncommon in inferolateral infarcts. Even when impairment of position sense is present, the ataxia shows characteristics that also suggest a cerebellar-type dysfunction. Delayed (weeks) dystonia and jerks may develop in the hand contralateral to the infarct, usually in patients with marked sensory loss and ataxia (thalamic hand and unstable ataxic hand).

Behavioral changes, such as executive dysfunction, and cognitive signs, such as aphasia, are often undiagnosed. Executive functions relate to planning, initiation, and regulation of goal-directed behavior, and their dysfunction can lead to long-term disability. In contrast to amnesia, they are not restricted to a specific thalamic structure (Carrera and Bogousslavsky, 2006). Executive dysfunction and affective changes were described in six of nine patients with inferolateral lesions (Annoni et al., 2003). Aphasia is rarely reported (Karussis et al., 2000), but in one study (Carrera et al., 2004), mild transcortical motor aphasia with reduced fluency was found in almost one-third of patients.

22.4.1.3.2.2. Paramedian infarcts

The paramedian territory is supplied by the thalamoperforating arteries, which originate from the first part of the PCA and involve mainly the dorso-median and intralaminar nuclei of the thalamus (Carrera and Bogousslavsky, 2006). When the tuberothalamic artery is absent, the thalamoperforating arteries may assume that vascular territory, and an infarct here may be devastating (Schmahmann, 2003) (Fig. 22.14). The classic syndrome of unilateral infarct associates acute loss or decrease of consciousness (usually transient), frequently followed by neuropsychological disturbances, with upward gaze limitation, but very few motor or sensory abnormalities (de Freitas and Bogousslavsky, 2002; Bogousslavsky et al., 1986a)

Bilateral paramedian infarcts are not uncommon, accounting for at least one-third of paramedian thalamic infarcts (Bogousslavsky et al., 1988c). The explanation for this is the frequent finding of a unilateral paramedian pedicle supplying the paramedian region on both sides. Neurological and neuropsychological disturbances are usually more severe and long-lasting than in cases of unilateral involvement. Peculiar behavioral/neuropsychological disturbances include akinetic mutism, "thalamic dementia," and loss of psychic self-activation or robot syndrome (de Freitas and Bogousslavsky, 2002).

Behavioral changes become apparent when the decreased level of consciousness resolves. They consist mainly of personality changes with disinhibited behavior associated with apathy, loss of self-activation, and amnesia. Several distinct personality changes with disinhibition syndromes have been reported. These patterns may be difficult to distinguish from psychiatric pathologies (Carrera and Bogousslavsky, 2006). Cyclical psychosis and manic delirium have been reported with paramedian strokes; patients show episodes of delirium, joking, inappropriate comments and extraordinary confabulations (Bogousslavsky et al., 1988a). After unilateral, but especially after bilateral infarcts, patients may become apathetic and aspontaneous, as if they have lost motor and affective drive. In patients with extensive involvement of the centromedian and parafascicular nuclei who appear awake, fail to respond, and become active after relevant stimuli, akinetic mutism should be suspected and may represent a severe form of loss of psychic self-activation. Dementia due to a single lesion is rare but can occur after thalamic lesion, especially in the case of bilateral paramedian or anterior lesions. The diagnosis is made when impaired attention, apathy, and poor motivation have resolved (Carrera and Bogousslavsky, 2006). Paramedian thalamic strokes have been known to associate with excessive daytime sleepiness (hypersomnia). Significant hypersomnia usually signifies either a bilateral thalamic lesion or a unilateral thalamic lesion extending to the subthalamus (Lovblad et al., 1997).

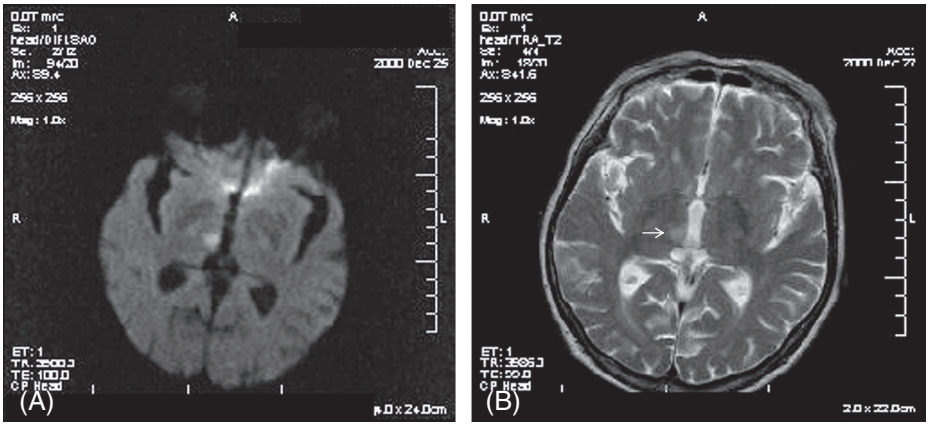

Fig. 22.14. A right-sided paramedian infarct shown by diffusion weighted MRI during the acute phase (A) and, 2 days later, by T2-weighted MRI (B).

22.4.1.3.2.3. Polar infarcts

The anterior, tuberothalamic, or polar territory is supplied by the tuberothalamic or polar artery, which originates from the posterior communicating artery or, in one-third of patients, at the paramedian or thalamoperforating arteries, and involves the anterior nuclei (Carrera and Bogousslavsky, 2006). Clinical dysfunction is mainly neuropsychological. Left-sided infarcts are associated with the same aphasic disturbances seen in "subcortical" aphasia in general, while right-sided infarcts are associated with hemineglect and impaired visuospatial processing (Bogousslavsky et al., 1986b; Bogousslavsky et al., 1988b). In a few instances, unilateral left or, more often, bilateral infarcts can result in acute amnesia as the main dysfunction. Sensorimotor disturbances, when present, are mild and transient.

Anterograde amnesia, with better performance for recognition, is a constant finding and may persist several years after stroke. In some cases, visuospatial impairment is prominent after right lesions and verbal impairment after left lesions (Clarke et al., 1994; Carrera and Bogousslavsky, 2006). In the early stages of infarct, patients exhibit fluctuating levels of consciousness and appear withdrawn. Persistent personality changes include disorientation in time and place, euphoria, lack of insight, apathy, and lack of spontaneity. Language disturbances occur in left hemisphere lesions, characterized by anomia with decreased verbal output and impaired fluency, impairment of comprehension, and fluent paraphasic speech that may be hypophonic and lack meaningful content (Schmahmann, 2003).

22.4.1.3.2.4. Posterior choroidal infarcts

The posterior territory is supplied by the medial and lateral branches of the posterior choroidal artery. The pulvinar is the main component of the posterior nuclei (Carrera and Bogousslavsky, 2006).

The following three neurological features are the most important symptoms of these infarcts: (1) visual dysfunction, including upper or lower quadrantanopia or, more typically, horizontal sectoranopia; (2) sensorimotor hemisyndrome; and (3) neuropsychological disturbances. Involuntary movements, such as acute-onset choreoathetosis, may also develop. Apparently, no specific behavioral syndrome results from a posterior lesion.

22.4.2. Basilar and vertebral arteries

22.4.2.1. Brain stem infarcts

22.4.2.1.1. Blood supply and vascular territories

These are shown in Fig. 22.15. The main arterial trunks supplying the brainstem include the VA, anterior spinal artery, posterior inferior cerebellar artery (PICA), basilar artery (BA), anterior inferior cerebellar artery (AICA), superior cerebellar artery (SCA), PCA, PCoA, and AChA. The collaterals of these arteries are divided into four arterial groups (anteriomedial, anterolateral, lateral, and posterior), which supply the brainstem (Tatu et al., 1996). The origin of the arterial supply varies at each level of the brainstem:

- Medulla:
  (1) the anteromedial and anterolateral groups arise from the VA and anterior spinal arteries;
  (2) the lateral group arises from the PICA, VA, BA, and AICA;
  (3) the posterior group arises from the PICA for the upper part of medulla and from the posterior spinal artery for the lower part.
- Pons:
  (1) the anteromedial and anterolateral groups arise from the BA;
  (2) the lateral group arises from the AICA and BA (lateral pontine arteries);
  (3) the posterior group arises from the SCA.
- Midbrain: the BA supplies the paramedian region, mainly its ventral part, the SCA supplies the lateral–dorsal region of the caudal two-thirds via its circumferential branches, and the contribution of the PCA increases caudorostrally, so that the upper half of the midbrain is supplied through direct branches from the distal BA and the proximal PCA. The PCA supplies the anteriomedial group (middle rami of the interpeduncular fossa). The collicular and posteromedial choroidal arteries are the main sources of the anterolateral and lateral groups; the posterior group is supplied by the SCA, collicular and posteromedial choroidal artery. The anterior choroidal and PCA may also supply the anterolateral group.

22.4.2.1.2. Medullary infarcts

These can be divided into medial and lateral medullary syndromes and a combination of both (hemimedullary infarct).

22.4.2.1.2.1. Lateral medullary infarct

22.4.2.1.2.1.1. Etiology and frequency Lateral medullary infarct, so called Wallenberg's syndrome, is one of the most common brainstem infarcts and accounts for about 2% of all admissions for acute stroke (Norrving and Cronqvist, 1991). It is caused mainly by occlusion of the VA and/or the PICA. Often, the occlusion is a result of atherosclerosis, but dissection of the VA may be an important cause in young patients (Vuilleumier et al., 1995).

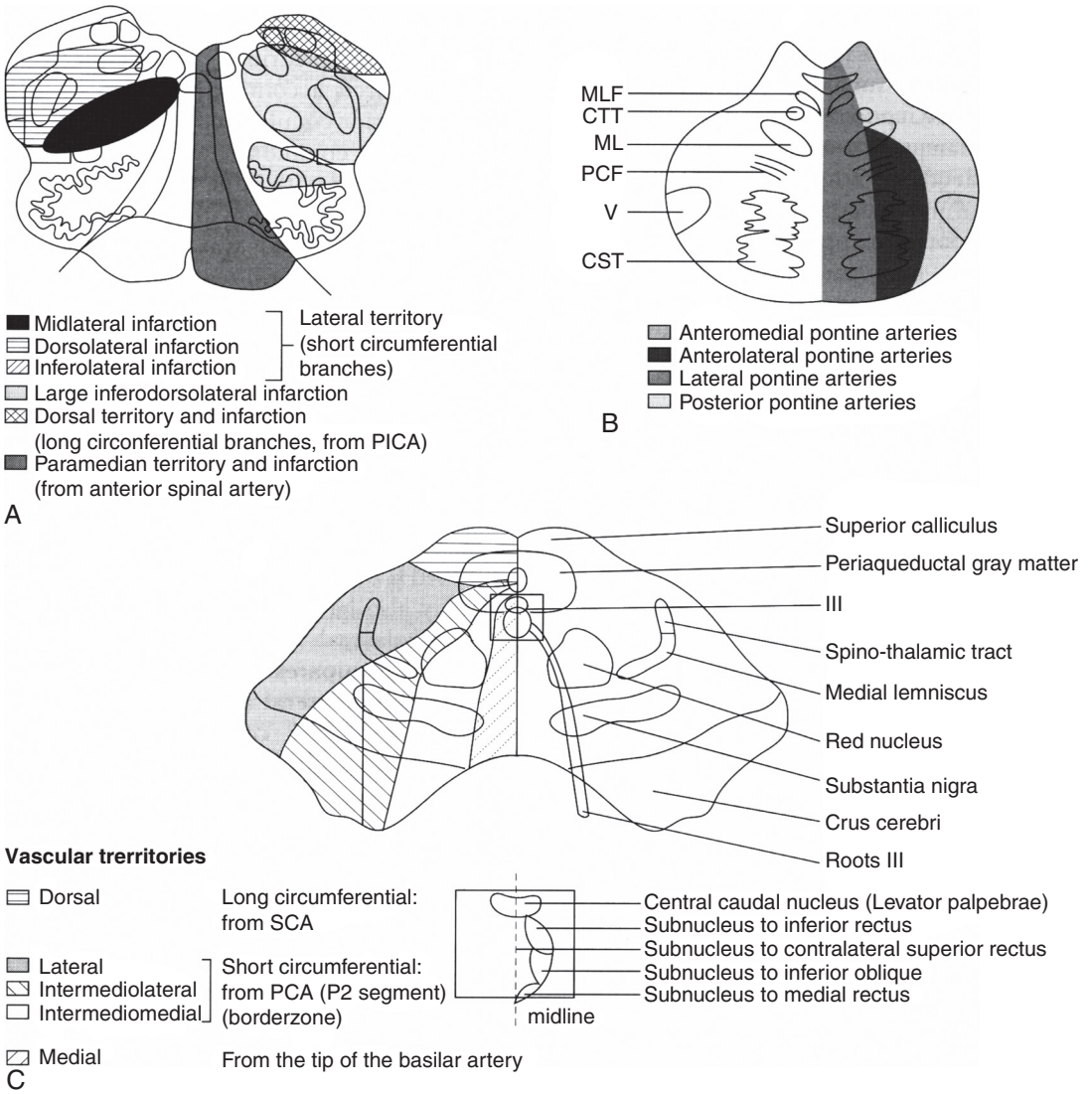

Fig. 22.15. Arterial supply to the medulla oblongata (A), upper middle pons (B), and middle midbrain (C). PICA = posterior and inferior cerebellar artery; CST = corticospinal tract; V = trigeminal nerve; PCF = pontocerebellar fibers; ML = medial lemniscus; CTT = central tegment tract; MLF = medial longitudinal fasciculus; III = oculomotor nerve; SCA = superior cerebellar artery; PCA = posterior cerebral artery.

22.4.2.1.2.1.2. Clinical features An ipsilateral Horner's syndrome (ptosis, miosis, enophthalmia, and loss of facial sweating) due to involvement of sympathetic fibers may be seen in up to 95% of patients, mainly in its incomplete form (Norrving and Cronqvist, 1991). Ipsilateral limb ataxia is also common, and is caused by a lesion of the spinocerebellar tracts or restiform body or by an accompanying cerebellar infarct. Ipsilateral sensory loss in the face always involves pain and temperature sensation, and light touch is also often affected (Currier et al., 1961), probably due to involvement of the nucleus of the descending tract of nerve V. The corneal reflex is often absent. Facial pain, usually described as burning, is common and is usually localized around the eye or over the whole face. Mild ipsilateral facial weakness may be seen in some patients, but its explanation is not clear. Dysarthria, dysphagia, and dysphonia may be seen as a result of ipsilateral vocal cord and palatal weakness due to involvement of the nucleus ambiguus. Contralateral sensory loss in the trunk and extremities may be present secondary to crossed spinothalamic tract involvement. Vertigo is common and is caused by a lesion in the vestibular nuclei or their connections. Many ocular abnormalities, such as nystagmus, skew deviation with ipsilateral hypotropia and diplopia, and ocular lateropulsion

toward the side of the infarct may be observed. Hiccups are sometimes present and are attributed to respiratory center involvement. It is not possible to predict whether there is an associated cerebellar infarct on the basis of the clinical examination alone. In one series, 11% of patients died during the acute phase from respiratory and cardiovascular complications (Norrving and Cronqvist, 1991).

22.4.2.1.2.2. Medial medullary infarct

22.4.2.1.2.2.1. Etiology and frequency Dejérine syndrome is relatively rare, appearing in one of 28 medullary infarcts in one series (Vuilleumier et al., 1995). The cause of the infarct is often atherothrombosis of the VA or the anterior spinal artery (Kim et al., 1995a).

22.4.2.1.2.2.2. Clinical features Contralateral hemiparesis (rarely ipsilateral) and a hemisensory deficit sparing the face are the most common symptoms (Kim et al., 1995a). Ipsilateral lingual paresis or clumsy tongue movements may occasionally be observed.

22.4.2.1.2.3. Hemimedullary infarct

Also called Reinhold's syndrome, this is rare (Vuilleumier et al., 1995; de Freitas et al., 2001) (Fig. 22.16). Although it was wrongly assumed that the Babinski–Nageotte syndrome corresponded to a lesion involving the hemimedulla, in fact it includes all symptoms of Wallenberg's syndrome and additionally contralateral hemiparesis (Krasnianski et al., 2003, 2006). The classic clinical picture of the hemimedullary syndrome is a combination of the symptoms of lateral and medial medullary infarcts. When the motor deficit is ipsilateral to the infarction, it may suggest that dissection of the VA is the mechanism of the stroke (Porto et al., submitted). While atherosclerotic burden usually predominates in the distal segment of the VA (Castaigne et al., 1973), dissection more frequently involves the second and third portion of the vessel (Arnold et al., 2006), therefore affecting the lower branches of the artery and provoking ipsilateral hemiparesis.

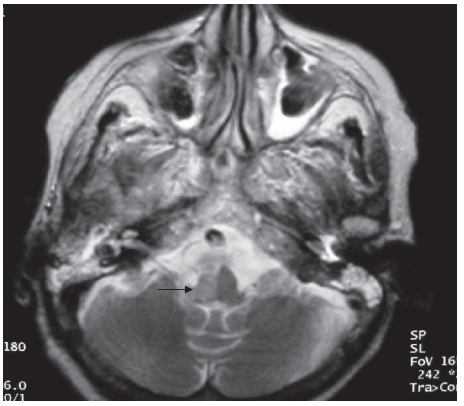

Fig. 22.16. T2-weighted MRI, showing an infarct involving the right hemimedulla (arrow) (de Freitas et al., 2001).

22.4.2.1.3. Pontine infarcts

22.4.2.1.3.1. Etiology and frequency

In a study performed by one of the present authors (Bogousslavsky), pontine infarcts accounted for 15% of the infarcts in the posterior circulation (Bassetti et al., 1996). BA branch disease was the most common cause of stroke (44%) and was associated with large ventral infarcts with severe clinical symptomatology (Fig. 22.17A). Small-artery disease (25%) was usually associated with small ventral or tegmental infarcts and rapidly improving lacunar syndromes (Fig. 22.17B) (Bassetti et al., 1996).

22.4.2.1.3.2. Clinical features

Pontine infarcts are classified into four main groups:

1. Ventromedial pontine infarcts, associated with moderate to severe hemiparesis, either alone (pure motor hemiparesis) or accompanied by homolateral ataxia (ataxic hemiparesis). Some patients may also exhibit contralateral crural ataxia.
2. Ventrolateral infarcts, often present as a mild hemiparesis, sometimes associated with homolateral ataxia (ataxic hemiparesis or pure motor hemiparesis). A variant of ataxic hemiparesis, called dysarthria clumsy-hand syndrome, is occasionally found (Kim et al., 1995b). Some patients may show mild signs of tegmental involvement, such as ocular abnormalities, vertigo, and sensory loss (sensorimotor stroke).
3. Tegmental pontine infarcts, possibly presenting as vertigo, diplopia, eye movement disturbances, cranial nerve palsies, truncal and extremities sensory loss, and mild motor deficits.
4. Bilateral ventrotegmental infarcts, associated with acute pseudobulbar palsy and uni- or bilateral sensorimotor dysfunction. Bilateral large ventral infarcts may cause the locked-in syndrome, characterized by tetraplegia, facial diplegia, pharyngeal palsy, and horizontal gaze palsy with normal consciousness, the patient only being able to communicate using a code involving blinking and moving the eyes up and down.

Short-term prognosis was good in two-thirds of patients in one study, including patients with isolated pontine infarcts (Bassetti et al., 1996). However, the subgroup of patients with large, ventral infarcts had a less favorable outcome, with good recovery in only one-third of cases.

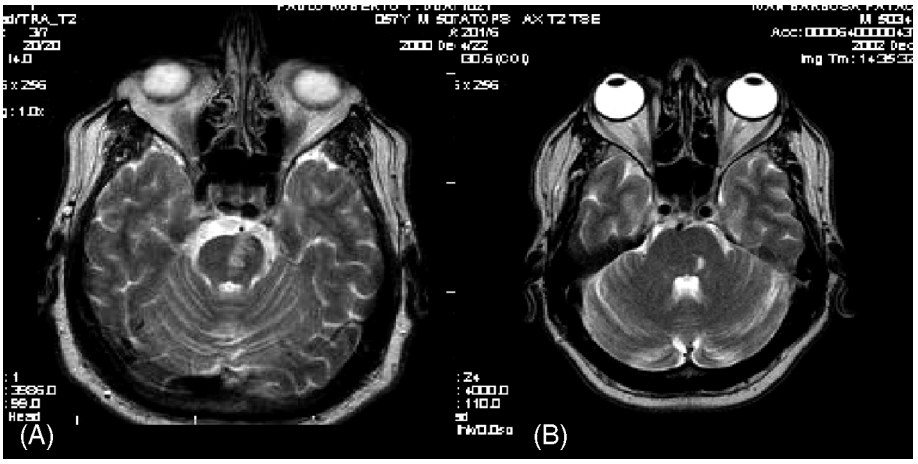

Fig. 22.17. (A) A 57-year-old hypertensive diabetic man presented with right hemiplegia and hemianesthesia involving the face, arm, and leg, severe dysarthria, and left extraocular palsy. The MRI showed a large pontine infarct caused by basilar atherosclerotic stenosis ("branch disease"). (B) A 62-year-old hypertensive man presented with a sudden painful feeling in his left eye and nose ("salt and pepper in the face" pain) and mild right hemiparesis. The MRI showed a small tegmental pontine infarct, probably caused by small-artery disease.

22.4.2.1.4. Midbrain infarcts

22.4.2.1.4.1. Etiology and frequency

These account for 8% of all infarcts in the posterior circulation (Bogousslavsky et al., 1994). BA disease (27%), cardio-embolism (23%), and small-artery disease (23%) were found to be equally common causes in a study performed in the LSR (Bogousslavsky et al., 1994).

22.4.2.1.4.2. Clinical features

Most infarcts are localized in the middle part of the midbrain, and are characterized by nuclear (bilateral ptosis, bilateral superior rectus weakness, or bilateral mydriasis) or peripheral (unilateral adduction/upward/downward palsy with ptosis and mydriasis) third nerve involvement, with or without hemiparesis. Infarcts in the upper or lower midbrain usually have no localizing findings, and often include a combination of ataxia and hemiparesis (ataxic hemiparesis or pure motor hemiparesis).

22.4.3. Cerebellar infarcts

22.4.3.1. Blood supply and vascular territories

These are shown in Fig. 22.18. The PICA arises from the terminal portion of the VA and gives rise to two branches, medial and lateral. It vascularizes the inferior vermis and the inferior and posterior surfaces of the cerebellar hemispheres. The medial branch also supplies the dorsolateral region of the medulla oblongata. The AICA arises from the caudal third of the BA and supplies the anterior surface of the simple and superior and inferior semilunar lobules, the flocculus, and the middle cerebral peduncle. It also supplies the lateral portion of the pons. The SCA arises from the rostral BA and divides into medial and lateral branches. It vascularizes the superior half of the cerebellar hemisphere and the vermis, including the dentate nucleus. The medial SCA also supplies a small portion of the brainstem, namely the laterotegmental region of the rostral pons and lower midbrain (Amarenco, 1991; Barth et al., 1993; Tatu et al., 1996).

22.4.3.2. Etiology and frequency

Cerebellar infarcts account for about 2% of all infarcts. PICA and SCA territory infarcts are equally frequent, accounting respectively for 47% and 38% of cerebellar infarcts (Barth et al., 1993). AICA territory infarcts are rarer. Some patients have cerebellar infarcts involving more than one territory, whereas others have infarcts in junctional areas. The etiology varies according to the territory affected. Most AICA infarcts are caused by BA atherosclerosis (Amarenco and Hauw, 1990a), whereas SCA infarcts are often caused by cardio-embolism. PICA infarcts are caused by cardio-embolism or VA atherosclerosis, depending on the branch affected (Barth et al., 1993).

22.4.3.3. Clinical features

22.4.3.3.1. PICA territory infarcts

When the medulla is involved, a typical Wallenberg's syndrome (see above) may be present. Infarcts of the whole PICA territory and the medial PICA territory manifest as rotatory vertigo, nausea, and vomiting (Fig. 22.19). Patients show signs of cerebellar dysfunction, with truncal ataxia and mild ipsilateral limb dysmetria. Patients with an isolated infarct in the territory of the lateral PICA present with cerebellar ataxia involving mainly the limbs, without trunk ataxia

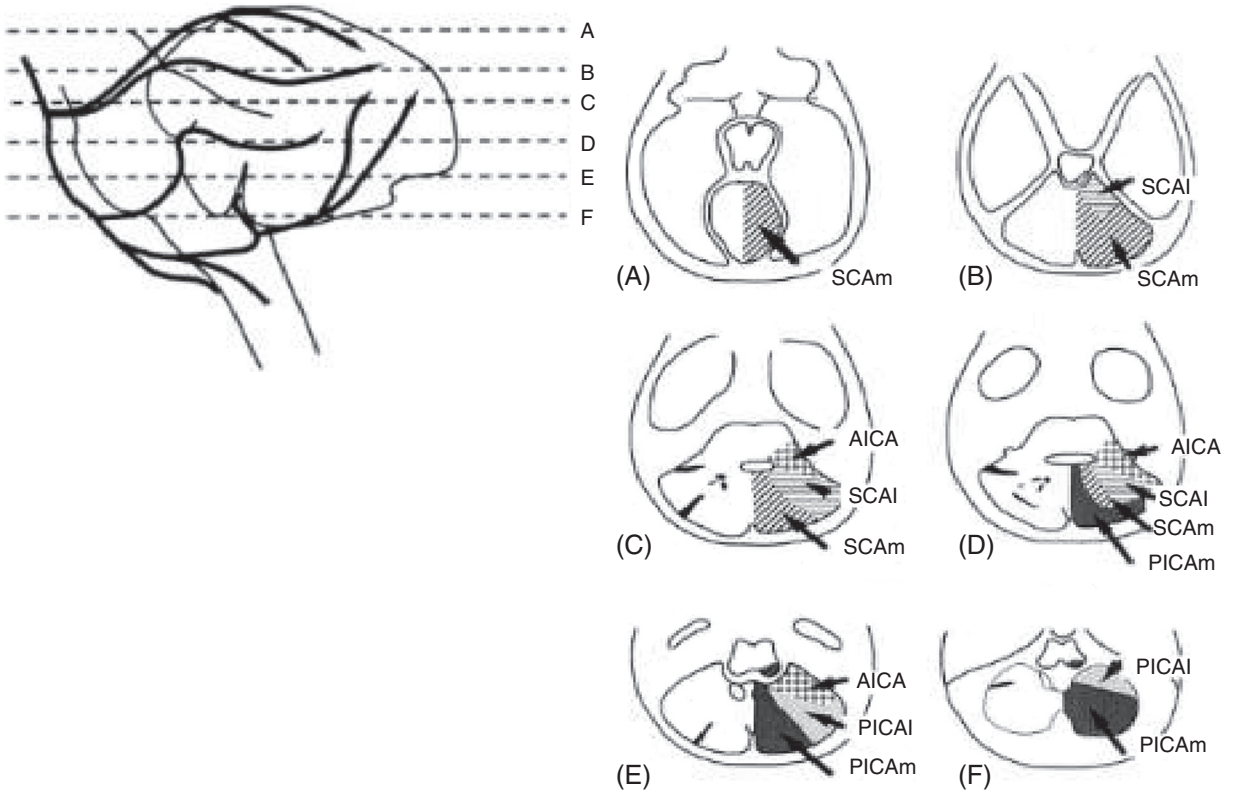

Fig. 22.18. Arterial supply to the cerebellum. SCAm = medial territory of the superior cerebral artery; SCAI = lateral territory of the superior cerebral artery; AICA = territory of the anterior and inferior cerebellar artery; PICAm = medial territory of the posterior and inferior cerebellar artery; PICAI = lateral territory of the posterior and inferior cerebellar artery (Amarenco, 1991).

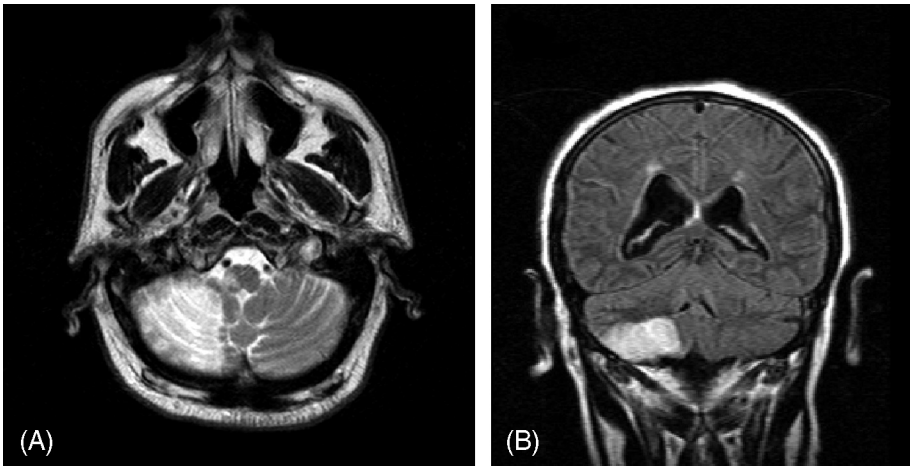

Fig. 22.19. MRI scan showing an infarct in the territory of the posterior and inferior cerebellar artery involving the cerebellum and the dorsolateral portion of the medulla.

(Barth et al., 1993). Cerebellar infarction mimicking vestibular neuritis, presenting with isolated vertigo, is more common than previously thought. The territory most commonly involved is the medial branch of the PICA territory (Lee et al., 2006).

22.4.3.3.2. AICA territory infarcts

Most patients have cranial nerve involvement (V, VII or VIII), Horner's syndrome, or contralateral temperature and pain sensory loss, indicating a concomitant lateral pontine lesion (Amarenco and Hauw, 1990a;

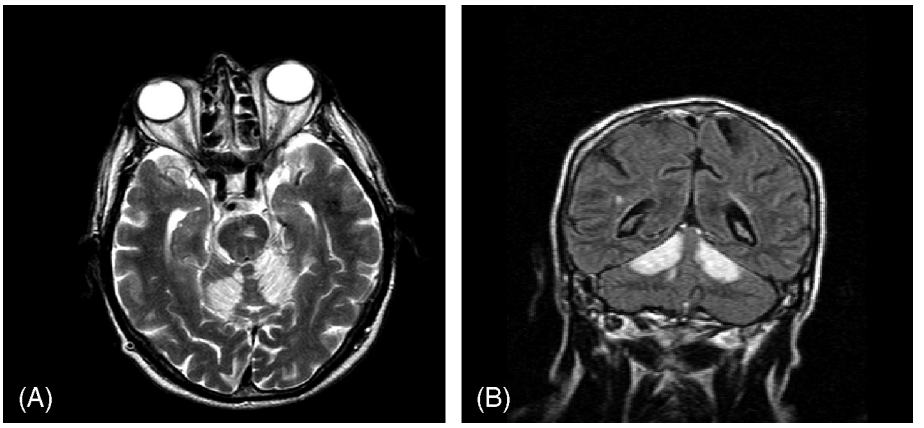

Fig. 22.20. Bilateral infarcts involving both superior cerebellar artery territories shown by MRI axial (A) and coronal (B) slices.

Amarenco et al., 1993). Vertigo and dysarthria may arise in AICA infarcts, sparing the pons.

22.4.3.3.3. SCA territory infarcts

Many patients have concomitant involvement of other territories and may present with a "top of the basilar syndrome," with a thalamic syndrome, behavioral changes, visual field defects, disorders of ocular movement, and hemi- or tetraparesia (Amarenco and Hauw, 1990b). In isolated cerebellar infarcts, presentation includes cerebellar dysarthria, unsteadiness or vertigo, nystagmus, and limb or trunk ataxia. When the dorsal mesencephalic territory of the SCA is involved, the rare, classic picture of limb ataxia, Horner's syndrome, IV nerve palsy, and contralateral sensory impairment will be present (Amarenco and Hauw, 1990b; Barth et al., 1993). Whole PICA and SCA territory infarcts (Fig. 22.20) and multiple territory infarcts may have a severe evolution, including brainstem compression, while the patient's condition may worsen toward deep coma.

22.5. Borderzone territories (watershed or borderzone infarcts)

22.5.1. Etiology and frequency

Infarct may develop at the collateral border zone between two main pial arterial territories. These extraterritorial infarcts, commonly called watershed infarcts, account for about 3% of the infarcts in the LSR (Table 22.1). Most watershed infarcts are in the anterior circulation, although they may also be present in the cerebellum, brainstem, and thalamus. The regions most often involved are the borderzones between the middle and anterior cerebral arteries (anterior watershed infarcts) and between the middle and posterior cerebral arteries (posterior watershed infarcts). Infarcts between the superficial and deep territories of the MCA are sometimes called subcortical watershed infarcts but, according to some authors, the term "subcortical junctional infarct" is more appropriate, since they occur between deep perforators which do not have collaterals, and the term "watershed" implies a borderzone between two pial territories, at the level of their collateral network.

The clinical evidence suggests that watershed infarcts are hemodynamic in nature, since events are commonly precipitated by an iatrogenic drop in blood pressure or standing up. Loss of consciousness is observed at stroke onset, with half of patients having an elevated hematocrit, while heart disease associated with hypotension is common (especially bradyarrhythmia), and most patients

Table 22.7

Watershed infarcts: main neurological features

Anterior watershed infarct
Hemiparesis with crural predominance (when infarct extends subcortically with proximal brachial predominance (when infarct mainly cortical)
Hemihypesthesia with the same distribution
Left-side infarct: transcortical motor aphasia (often after initial mutism)
Right-side infarct: motor hemineglect, apathy, euphoria, anosognosia (disputable)
Bilateral: bilateral diplegia or "man-in-the-barrel" syndrome
Posterior watershed infarcts
Cortical hemihypoesthesia with faciobrachial predominance
Lateral hemianopia or upper quadrantanopia
Left side infarct: transcortical sensory aphasia or isolated anomia
Right side infarct: spatial hemineglect, anosognosia

From de Freitas and Bogousslavsky (2005).

have occlusions or severe obstructions of the ipsilateral (Bogousslavsky and Regli, 1986a) and contralateral ICA (Bogousslavsky and Regli, 1986b). However, embolism may be responsible in some cases and, in many instances, both embolism and hypoperfusion may play a role (Caplan and Hennerici, 1998). The clinical features are summarized in Table 22.7.

22.6. Conclusion

Knowledge of clinical syndromes resulting from the involvement of arterial territories is essential for all neurologists, but especially for those dealing with neurological emergencies, cerebrovascular diseases, or behavior abnormalities. The early identification of the artery involved and the respective mechanism of ischemia may have implications for therapeutic management and determine the investigations to be carried out. Clinicoradiological correlations using new techniques, such as diffusion and perfusion MRI, may help to provide a better delineation of the anatomy of brain functions.

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Chapter 23

Identification, risks, and treatment of transient ischemic attack

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23.1. Introduction

Transient ischemic attack (TIA), like stroke, is characterized by the acute onset of focal cerebral ischemia, and TIA and completed stroke are largely indistinguishable on the basis of etiology, diagnostic evaluation, and secondary prevention (Feinberg et al., 1994; Albers et al., 1999; Wolf et al., 1999). However, the two syndromes also have important distinguishing characteristics that affect prognosis and acute management; in particular, TIA is associated with a higher short-term risk of additional ischemic events than stroke and, by definition, patients with TIA are neurologically unimpaired.

Our understanding of TIA and its implications has evolved substantially over the past decades, a process that continues and extends to how the term and the clinical entity are defined. In this chapter we will review current approaches to identifying and evaluating the patient with TIA, the burden of TIA from a public health perspective, the risk of subsequent cerebro- and cardiovascular events following TIA, and the current standards of management and secondary prevention. Framing this information, we will discuss the debate over how best to define a TIA, including attempts to identify the features of TIAs that may have the most importance to the clinician and the patient in terms of predicting future risk and preventing future events.

23.2. Definition

Over the years, ischemia with reversible symptoms has been classified into a number of different syndromes based in part on the duration of symptoms (Wiebers et al., 1982; Waxman and Toole, 1983; Calandre et al., 1984; Dávalos et al., 1988; Toole, 1991), and the definition of TIA has been debated and has evolved (Caplan, 1983; Waxman and Toole, 1983; Calandre et al., 1984; Warlow, 1985; Dennis et al., 1989a, b; Toole, 1991; Kimura et al., 1999). The definition of TIA that is used most frequently—a neurological deficit of abrupt onset that is attributable to focal ischemia and resolves completely within 24 hours—is based on a report published 30 years ago by the Ad Hoc Committee of the Advisory Council for the National Institute of Neurological and Communicative Disorders and Stroke (Anonymous, 1975). A previous definition put forth by the same group in 1958 (Ad Hoc Committee on Cerebrovascular Disease, 1958) limited TIAs to episodes resolving within 1 hour, but also included migraine as a type of transient cerebral ischemia.

Duration is a logical choice for distinguishing events because shorter episodes tend to have less impact on patient wellbeing, but the requirement that symptoms resolve completely within a given time is arbitrary. Symptom duration does not reflect the underlying pathology (Humphrey and Marshall, 1981) and is only imperfectly correlated with neurological impairment (Kimura et al., 1999) and risk of subsequent stroke (Humphrey and Marshall, 1981; Johnston et al., 2000; Rothwell et al., 2005). In fact, both of the definitions from the Ad Hoc Committee were predicated on the assumption that ischemia that resolved quickly enough to cause only transient symptoms was unlikely to have caused permanent brain injury or infarct, a quite reasonable assumption in the days before computed tomography

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(CT) or magnetic resonance imaging (MRI). A more recent classification (Anonymous, 1990) recognizes that TIAs are often associated with cerebral infarct, defining TIA as

> *Brief episodes of focal loss of brain function, thought to be due to ischemia, that can usually be localized to that portion of the brain supplied by one vascular system . . . and for which no other cause can be found. Arbitrarily, by convention, episodes lasting <24 hours are classified as TIAs, although the longer the episode the greater the likelihood of finding a cerebral infarct by CT or MRI.*

This definition also acknowledges that there are "unusual instances that fall outside this definition."

A lively debate has emerged surrounding how to refine this definition based on advances in diagnostic techniques, management, and secondary prevention, and the emerging evidence that TIA, far from being a benign event, is a harbinger of more serious events and demands urgent and thorough attention. The largest debate has been whether the presence of an infarct on head imaging should be used to distinguish stroke from TIA, whether the entity of TIA should continue to be based on duration alone, or even whether the presence of an infarct and transient symptoms characterizes a unique syndrome distinct from TIA or stroke (Waxman and Toole, 1983; Bogousslavsky and Regli, 1985; Dennis et al., 1990b; Koudstaal et al., 1991; Toole, 1991; Eliasziw et al., 1995; Kimura et al., 1999; Albers et al., 2002; Ay et al., 2005). A number of studies have detected infarctions in patients with TIA (Dávalos et al., 1988; Evans et al., 1991; Kidwell et al., 1999; Kimura et al., 2000; Eliasziw et al., 2004; Inatomi et al., 2004; Purroy et al., 2004; Warach and Kidwell, 2004; Winbeck et al., 2004), with the frequency of infarct increasing with the duration of symptoms (Koudstaal et al., 1992; Engelter et al., 1999; Kidwell et al., 1999; Crisostomo et al., 2003; Inatomi et al., 2004); however, acute infarcts have also been detected in patients with TIAs lasting less than 1 minute (Koudstaal et al., 1992; Crisostomo et al., 2003), and even brief occlusion of large arteries causing transient symptoms may produce permanent cell injury (del Zoppo, 2004). TIA with and without infarct cannot generally be distinguished clinically (Koudstaal et al., 1991), although they may be associated with different prognoses (Ay et al., 2005).

In 2002, the TIA Working Group proposed a new definition (Albers et al., 2002) that explicitly separated TIA from cerebral infarction: "A transient ischemic attack is a brief episode of neurologic dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting less than one hour, and without evidence of acute infarction."

This definition more closely mirrors the way that cardiac ischemia is categorized, and by limiting the duration to 1 hour reduces the chance that a treating physician will wait hours for symptoms to resolve rather than proceeding with urgent evaluation and emergent treatment (Albers et al., 2002). However, the definition is also predicated on the availability of brain imaging, which is not always performed and varies in sensitivity. Thus, the same event may be classified differently based on whether and what type of imaging is performed, and it is not clear that the presence of acute infarction is important to the patient or should affect management decisions (Koudstaal et al., 1991; Eliasziw et al., 1995). Furthermore, it is not clear that a TIA resolving within 1 hour is truly a different entity from one lasting 2 or 3 hours, and treatment and prognosis are unlikely to differ.

A functional definition (Caplan, 1983) that included the cause of the ischemia, the anatomy involved, and the severity of the functional deficits would shift the focus away from terminology and toward patient management. It may also be important to consider whether significant early recovery has occurred, even if some residual symptoms remain, rather than whether symptoms have fully resolved at any particular time point (Humphrey and Marshall, 1981; Johnston and Easton, 2003; Johnston et al., 2003b). Patients with rapid recovery have a high incidence of deterioration within the day or several days following treatment (Alexandrov et al., 2000; Grotta et al., 2001). A definition that included the degree of rapid recovery in addition to other functional descriptors would reflect the instability of the underlying lesion, and would emphasize the urgency of evaluation and intervention for this subset of patients.

23.3. Identifying and diagnosing TIA

Even were there to be consensus on the proper definition of TIA, obtaining a definitive diagnosis can be a challenge, as there is no objective indicator of TIA that is both sensitive and specific. TIA is differentiated from ischemic stroke by the duration of symptoms, but the short duration of TIAs means that, in many cases, the symptoms have resolved by the time the patient reaches a physician or the emergency department (Douglas et al., 2003; Inatomi et al., 2004). The diagnosis must then be based primarily on the recollections of the patient or the patient's companions, who may have been too frightened or distracted to remember details with much accuracy. One report (Koudstaal et al., 1989), however, suggested that

patient reports are generally reliable and it is the physician's interpretation of patient descriptions that adds variability to diagnosis. Agreement between treating physicians, even neurologists, is limited as to whether an individual event was a TIA (Tomasello et al., 1982; Kraaijeveld et al., 1984; Koudstaal et al., 1989; Martin et al., 1997), and agreement is particularly poor between primary care physicians and specialists (Ferro et al., 1996; Gibbs et al., 2001). Neurological training, unambiguous symptoms, and examination while the symptoms are ongoing improve the reliability of the diagnosis (Calanchini et al., 1977). Several proposals have been made for ways to increase the reliability of diagnosis, including questionnaires (Wilson et al., 2005), a checklist in ordinary language (Koudstaal et al., 1986) and the use of an algorithm (Toole et al., 1996). However, these methods still rely on physicians to base their diagnoses on published criteria for TIA, which they do not always do (Koudstaal et al., 1986). Increasing the reliability of diagnosis may therefore depend in part on educating physicians.

23.3.1. Differential diagnosis

It is important to differentiate true ischemic events from nonischemic events (TIA mimics). Patients with transient symptoms not due to ischemia should not be subjected to the expense and risk of invasive diagnostic procedures and may be harmed by treatments such as anticoagulation, which are contraindicated in patients with subdural hematoma, aneurysm, and other conditions that can mimic TIA. Conversely, those with true TIA need to be evaluated and treated urgently.

The symptoms of TIA can be produced by a number of other syndromes, including syncope, migraine (Fisher, 1980; Wijman et al., 1998), vasospasm (Burger et al., 1991), seizures (Lee and Lerner, 1990), systemic infections (Libman et al., 1995), or hyperventilation due to anxiety (Koudstaal, 1993; Bots et al., 1997). Space-occupying lesions, such as subdural hematoma (Mishriki, 1999) and tumors, can also lead to transient neurological symptoms, including aphasia (Mishriki, 1999). Migraine can be particularly difficult to differentiate from TIA in older adults. The non-headache symptoms of migraine, known as "accompaniments," are usually associated with migraine in younger individuals, but may occur without headache in patients over 40 years old, even in those with no previous history of migraine (Fisher, 1980; Wijman et al., 1998).

Certain clinical symptoms are more indicative of etiologies other than TIA, including a march of symptoms in which different parts of the body are affected in succession; "positive" symptoms such as seizure or migraine accompaniments; incontinence; or altered consciousness, syncope, dizziness, amnesia, or confusion in isolation. True TIAs have a sudden onset (no symptoms to maximal symptoms in less than 5 minutes [Anonymous, 1990]) and usually have negative, loss-of-function symptoms limited to a specific vascular territory.

23.3.2. Tests and evaluation

Although the diagnosis of TIA is primarily a clinical one based on history and physical examination, a thorough evaluation can rule out alternative diagnoses (Gotshall et al., 1978) and establish the likely etiology (Culebras et al., 1997). The goal of the evaluation should be to identify the underlying causes of the TIA, to assess the immediate and long-term risk, and to institute appropriate treatments for the prevention of subsequent events. The work-up should thus be guided by the individual patient's symptoms and history, and diagnostic procedures should only be performed if they will contribute to management decisions, with cost and risk being taken into account. A summary of guidelines for the evaluation of TIA can be found in Table 23.1.

The initial evaluation will include a history and physical examination, routine laboratory tests, brain imaging, and electrocardiogram (ECG). Laboratory tests may include measurement of sodium and glucose levels, hematocrit, white-cell count, and platelet count, with other tests conducted on the basis of clinical history; the results may be useful to rule out metabolic or hematologic causes of the symptoms, such as hypoglycemia, hyponatremia, and thrombocytosis. Further tests will depend on the likely source of the ischemia, which can be determined based on the affected area of circulation as identified by the clinical symptoms (Fig. 23.1) and the results of brain imaging.

23.3.2.1. Diagnostic brain imaging

Brain imaging, including CT and various forms of MRI, is playing an increasingly large role in the diagnosis and evaluation of TIA. The presence of a new focal infarct on imaging can identify an event as ischemic in origin, locate the affected region, and rule out other causes of the symptoms such as a space-occupying lesion or hemorrhage (Hankey and Warlow, 1992; Mishriki, 1999; Douglas et al., 2003). There is now general consensus that brain imaging should be used in patients with the symptoms of TIA (Feinberg et al., 1994; Culebras et al., 1997). However, imaging is still not universally available (Gladstone et al., 2004) or universally used for all TIA patients (Goldstein et al., 2000; Douglas et al., 2003; Daffertshofer et al., 2004).

Table 23.1

Consensus guidelines for the care of patients with TIA*

Intervention	American Heart Association	National Stroke Association
Evaluation	Prompt evaluation	Evaluation within hours of symptom onset
Hospitalization	No recommendation	Recommended if appropriate imaging studies are not immediately available
Laboratory testing	Determined by history, to identify etiologies of TIA requiring specific therapies, to assess modifiable risk factors, and to determine prognosis	No specific recommendation
Electrocardiogram	Recommended	Recommended
Head imaging	CT in all patients; routine use of MRI not recommended due to higher cost and lower tolerability	No specific recommendation
Carotid imaging	Prompt ultrasound, MR angiography, or CT angiography	Urgent evaluation not further specified
Antithrombotic medications		
Cardio-embolic etiology	No specific recommendation on short-term use of heparin; long-term oral anticoagulation for patients with atrial fibrillation	Acute anticoagulation can be considered (modest supportive evidence)
Non-cardio-embolic etiology	Antiplatelet therapy with aspirin (50–325 mg/day), clopidogrel, ticlopidine, or aspirin-dipyridamole. Anticoagulation not generally recommended.	Antiplatelet therapy with aspirin (50–325 mg/day); consider clopidogrel, ticlopidine, or aspirin-dipyridamole in those who are intolerant of aspirin or had the TIA while taking aspirin. Anticoagulation not generally recommended.
Carotid endarterectomy	Recommended for good surgical candidates with 70–99% stenosis with TIA during prior 2 years; consider for patients with 50–69% stenosis based on clinical features that influence stroke risk and surgical morbidity. Timing not discussed.	Recommended without delay for those with symptomatic stenosis 50–99%
Risk factor management		
Hypertension	Maintain systolic blood pressure below 140 mmHg and diastolic blood pressure below 90 mmHg; for persons with diabetes, maintain systolic blood pressure below 130 mmHg and diastolic blood pressure below 85 mmHg	
Diabetes	Maintain fasting blood glucose levels below 126 mg/dL	
Hyperlipidemia	Diet and/or lipid-lowering agent with goal to maintain LDL cholesterol less than 100 mg/dL	
Cigarette smoking	Counseling, nicotine replacement therapies, and bupropion to support cessation	
Physical activity	Exercise 30–60 min three or more times per week	
Alcohol consumption	Formal alcohol cessation programs to eliminate excessive use; mild to moderate use (1–2 drinks/day) may be beneficial	
Obesity	Diet and exercise to reduce weight to less than 120% of ideal weight for height	

*Data are from the American Heart Association (Feinberg et al., 1994; Culebras et al., 1997; Albers et al., 1999; Wolf et al., 1999) and National Stroke Association (Brott et al., 2000). National Stroke Association guidelines were limited to acute management. TIA = transient ischemic attack. Reprinted from Johnston et al, 2002 with permission from Massachusetts Medical Society.

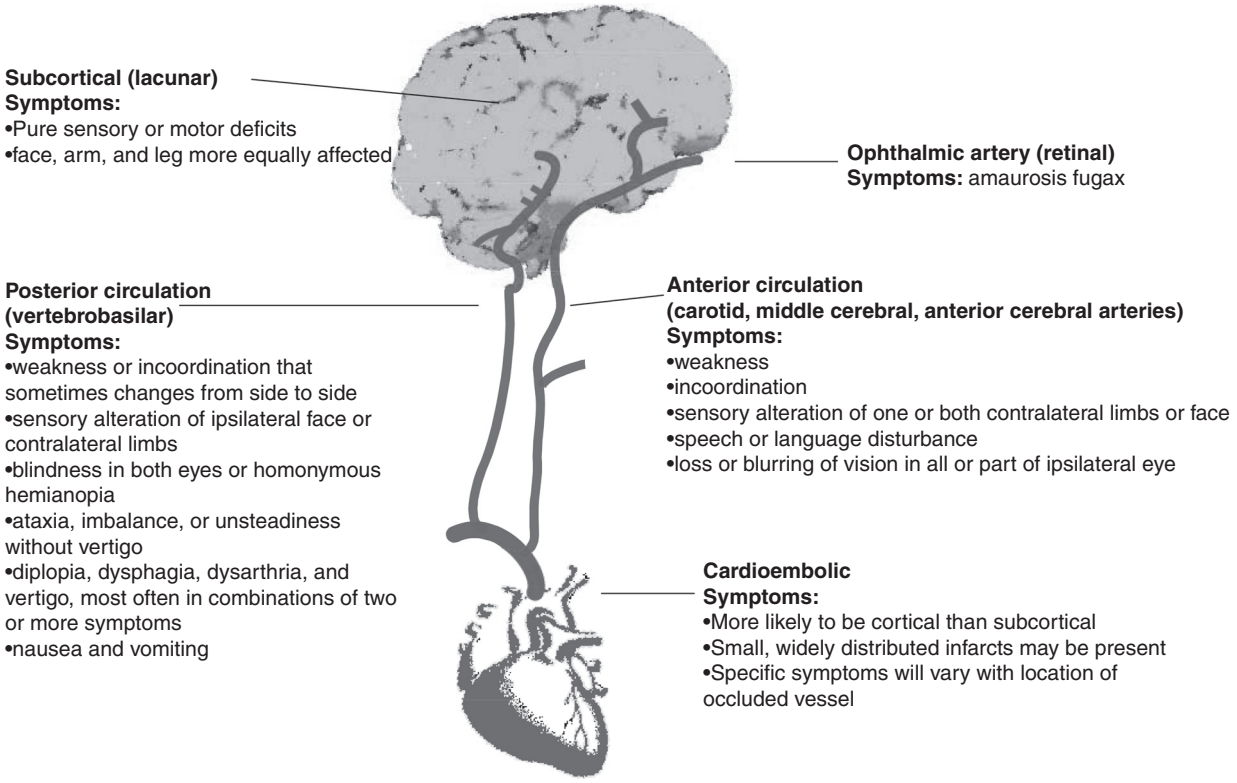

Fig. 23.1. Symptoms associated with common sources of transient ischemia. The selection of diagnostic tests and treatments may depend in part on the source of the ischemia. The pattern of symptoms, which varies with the affected vasculature, can help to identify the source.

Studies using various brain imaging techniques have revealed that infarction is not uncommon in patients with clinically defined TIA (Dávalos et al., 1988; Evans et al., 1991; Winbeck et al., 2004). Although the reported incidence of infarction has increased with the advent of newer and more sensitive techniques (Kimura et al., 2000; Eliasziw et al., 2004), it remains below 50% (Kidwell et al., 1999; Inatomi et al., 2004; Purroy et al., 2004; Warach and Kidwell, 2004; Winbeck et al., 2004); therefore, imaging is not a sensitive enough marker to rule out an ischemic event if it is negative.

Although the most recent guidelines (Culebras et al., 1997) recommend CT over MRI, MRI has since been shown to be superior to CT in reliably identifying small lesions (Awad et al., 1986; Fiebach et al., 2002). Diffusion-weighted magnetic resonance imaging (DWI) is more sensitive and specific than both standard CT and MRI (Kidwell et al., 1999) and can detect even very small lesions before T2-weighted imaging or other techniques (Gass et al., 2004). Acute lesions appear as high-contrast hyperintense regions in the first few days after the event, then fade away over the following weeks (Gass et al., 2004). As a result, DWI is most effectively used within 2 days of symptom onset (Crisostomo et al., 2003) because lesions that are visible during the acute period can resolve, and may no longer be visible on follow-up images (Kidwell et al., 1999; Inatomi et al., 2004); however, some have found DWI to provide additional information over T2 MRI for at least 2 weeks after the TIA (Schulz et al., 2004). The increased sensitivity of DWI can clarify the affected vascular territory or suspected etiology, providing information that is useful for further evaluation and treatment (Gass et al., 2004; Schulz et al., 2004). Kidwell and colleagues (Kidwell et al., 1999) found that DWI changed the suspected etiology of the ischemia in more than one-third of patients with visible lesions. The addition of other modalities to DWI, including apparent diffusion coefficient maps (Winbeck et al., 2004), perfusion-weighted imaging (Restrepo et al., 2004), and suppression of the cerebrospinal fluid signal (Bykowski et al., 2004), has further added to the ability of DWI to identify new infarcts and even to distinguish between reversible and irreversible ischemia (Bykowski et al., 2004; Winbeck et al., 2004).

As with CT (Koudstaal et al., 1992), the likelihood of seeing an infarct on DWI increases with the duration

of symptoms (Engelter et al., 1999; Kidwell et al., 1999; Crisostomo et al., 2003; Inatomi et al., 2004). However, lesions can also be apparent in some patients with very short duration of symptoms—one study found DWI abnormalities in 10% of those with symptom duration of less than 5 minutes, including one patient with symptoms lasting only 40 seconds (Crisostomo et al., 2003)—and the probability of a TIA being associated with a lesion drops off sharply if symptoms last more than a few hours (Ay et al., 2005). Although infarcts tend to be smaller with TIA than with ischemic stroke (Kidwell et al., 1999; Ay et al., 2005), the presence of a new infarct is associated with increased short-term risk of stroke in patients with the clinical symptoms of TIA (Douglas et al., 2003; Daffertshofer et al., 2004; Eliasziw et al., 2004), particularly if the symptoms last more than 1 hour (Purroy et al., 2004).

23.3.2.2. Other tests and evaluation

Further testing is aimed at confirming the source of the ischemia and the suitability of the patients for specific therapies. In patients suspected of having a TIA of anterior (carotid) distribution, evaluation of the degree of carotid stenosis should be performed urgently because endarterectomy can reduce the high risk of stroke in patients with severe stenosis.

The established gold standard for evaluation of carotid stenosis is catheter angiography, or digital subtraction angiography (DSA). However, DSA is expensive, invasive, and can itself precipitate ischemic events (Hankey and Warlow, 1992; Buskens et al., 2004). Noninvasive options include CT or MR angiography and carotid ultrasonography. CT angiography is sensitive and specific for carotid disease and can be performed at the same time as the recommended CT imaging during the acute evaluation (Josephson et al., 2004). MR angiography does not require contrast dye, but is expensive (Flemming et al., 2004). Carotid ultrasonography provides lower spatial resolution and higher error rates than DSA (Johnston and Hill, 2004; Shah and Edlow, 2004), but is cost-effective in identifying patients suitable for carotid endarterectomy (Buskens et al., 2004). The same angiographic techniques can also be used to examine stenosis of the posterior circulation.

In nearly all patients with TIA, it is appropriate to test for cardiac sources of ischemia. The simplest of these tests is the ECG, which is recommended for all patients with TIA (Feinberg et al., 1994). An ECG can indicate a cardio-embolic source such as atrial fibrillation or recent myocardial infarction (Pop et al., 1994; Elkins et al., 2002). Because atrial fibrillation can be intermittent in patients with cerebral ischemia, longer (7-day) ECG monitoring may be considered in patients with normal findings on standard and Holter ECGs (Jabaudon et al., 2004). If the cause of the TIA is still unknown after ECG, transthoracic or transesophageal echocardiography can be used to identify other sources of cardio-embolism (Hankey and Warlow, 1992; Flemming et al., 2004; Shah and Edlow, 2004; Yahia et al., 2004).

23.4. Burden of illness

Stroke represents a tremendous burden to society, both in personal terms (Matchar, 1998) and in economic costs (Gubitz et al., 1999; Reed et al., 2001). Each year more than 600,000 people in the USA alone will suffer an ischemic stroke. About 10% will die within 30 days, and 15–30% of survivors will be permanently disabled (American Heart Association, 2004). Research suggests that 15–19% of patients with completed stroke have suffered a previous TIA (Brainin et al., 1995; Johnston et al., 2003c); if strokes could be prevented in patients with TIA, the impact could be enormous.

Estimates of incidence and prevalence of TIA are likely to be highly dependent on the methodology and definition of TIA used to identify cases. Underreporting of TIA is a significant problem. Many cases, perhaps sometimes even a majority, are not brought to the attention of the medical system (Dennis et al., 1989b; Shelton and Gaines, 1995; Toole et al., 1996; Gibbs et al., 2001; Johnston et al., 2003c), due in part to the failure of many to understand the serious nature of TIA and stroke (Williams et al., 1997; Johnston et al., 2003c). As with other critical illnesses (Rodriguez et al., 2001), the resolution of symptoms in TIA is often perceived as a sign that urgent evaluation is not needed.

As a result of underreporting, studies based on medical registries (Dennis et al., 1989b; Lauria et al., 1996; Sempere et al., 1996) tend to report lower incidences, in the tens per 100,000 population, whereas those relying on survey methodologies (Fratiglioni et al., 1989; Matias-Guiu et al., 1994) report higher incidence rates into the hundreds per 100,000 population. The true value likely lies in between (Gibbs et al., 2001). Estimates of the prevalence of TIA have ranged from 1.1–6.3% in the USA (Karp et al., 1973; Ostfeld et al., 1973; Wilkinson et al., 1979; Phillips et al., 1990; Mittelmark et al., 1993; Chambless et al., 1996; Toole et al., 1996), and were reported to be as low as 0.2% for those aged 40 or over in a town in western Japan (Urakami et al., 1987). A recent nationwide telephone survey in the USA found that 2.3% of the more than 10,000 participants had a physician diagnosis of TIA (Johnston et al., 2003c), corresponding to a prevalence of approximately 4.9 million people in the USA; an equal number had been diagnosed with stroke. Given the similarities in the

prevalence of stroke and TIA (Toole et al., 1996; Johnston et al., 2003c) and the failure of patients to seek medical attention for symptoms consistent with TIA, the true incidence of TIA is probably similar to or greater than that of stroke. If TIAs with infarct were reclassified as stroke, estimates of TIA incidence would decrease and estimates of stroke incidence would increase (Ovbiagele et al., 2003); however, it is not clear what practical effects this would have.

In the USA, the community of Rochester, Minnesota, has been particularly well represented in reports of incidence (Whisnant et al., 1973; Phillips et al., 1990; Brown et al., 1998) because of the interconnected medical reporting system of the Mayo Clinic and other hospitals in the community, although some (Broderick et al., 1998) have maintained that the numbers reported for Rochester may not be representative of the USA as a whole because the residents of Rochester are predominantly white and affluent, and rates of TIA and stroke have been found to vary with racial and socioeconomic group (Karp et al., 1973; Johnston et al., 2003c; Kleindorfer et al., 2005). A report from Rochester covering the late 1980s (Brown et al., 1998) put the overall incidence of TIA at 68 per 100,000 population, including 13 cases of amaurosis fugax, 38 of anterior cerebral TIA, and 15 of vertebrobasilar TIA per 100,000 population. Although some studies have found a similar predominance of TIAs of carotid distribution (Dennis et al., 1989b), others have not (Ostfeld et al., 1973; Urakami et al., 1987; Fratiglioni et al., 1989). An increase in TIA incidence with age is seen consistently across studies (Whisnant et al., 1973; Fratiglioni et al., 1989; Lai et al., 1990; Johnston et al., 2003c). The number of people older than 65 grows by more than a half-million each year in the USA (Phillips et al., 1990), and the incidence of TIA and the burden of stroke are likely to rise as life expectancy increases; however, an increased emphasis on prevention and reduction of risk factors may offset the effect of the aging population to actually decrease the incidence of stroke (Rothwell et al., 2004c).

Although the costs for each patient who is hospitalized are considerably less for TIA than for stroke (Gubitz et al., 1999), they are still substantial; one study found an average of $3350 over 3.4 days of hospitalization for TIA, as compared to $5837 over 5.9 days of hospitalization for completed stroke (Reed et al., 2001). Overall, stroke costs the USA $35 billion in direct costs annually (American Heart Association, 2004), and the average cost per patient is $15,000 in the first 90 days after a stroke (National Institute of Neurological Disorders and Stroke, 2004). If hospitalization could prevent stroke in patients with TIA, it could reduce the overall economic burden. Hospitalization could also increase the likelihood that tissue plasminogen activator (tPA) would be administered in the event of a subsequent stroke; whether this would result in net cost savings depends on the absolute risk of stroke and the cost of hospitalization (Nguyen-Huynh and Johnston, 2005).

23.5. The high short-term risk of ischemic events after TIA

23.5.1. Risk of cerebral ischemia after TIA and completed stroke

It has long been recognized that TIA can presage a completed stroke (Ad Hoc Committee on Cerebrovascular Disease, 1958; Friedman et al., 1969), and the evidence is now overwhelming that risk of completed stroke after TIA is high in both the long-term (Canadian Cooperative Study Group, 1978; Muuronen and Kaste, 1982; Sorensen et al., 1989; Calandre et al., 1990; Dutch TIA Trial Study Group, 1991; Hankey et al., 1991; Kernan et al., 1991; Hankey et al., 1992; EAFT Study Group, 1993) and the short-term (Whisnant et al., 1973; Humphrey and Marshall, 1981; Putman and Adams, 1985; Biller et al., 1989; Dennis et al., 1990a; Johnston et al., 2000; Coull et al., 2004; Daffertshofer et al., 2004; Eliasziw et al., 2004; Hill et al., 2004; Kleindorfer et al., 2005) (Table 23.2).

Most hospital-based (Johnston et al., 2000; Daffertshofer et al., 2004; Eliasziw et al., 2004; Hill et al., 2004), population-based (Whisnant et al., 1973; Kleindorfer et al., 2005), and observational studies (Humphrey and Marshall, 1981; Putman and Adams, 1985; Coull et al., 2004; Gladstone et al., 2004), as well as one pilot trial (Biller et al., 1989), have demonstrated high short-term risks of stroke after TIA, well above those expected in cohorts of a similar age (Brown et al., 1996; Broderick et al., 1998). A prospective study of 612 patients in Texas (Lisabeth et al., 2004) found a lower 90-day risk of any stroke following TIA, 4%, than was seen in other studies. A population-based study (Dennis et al., 1990a) reported a risk of 4% in the first month, but events occurring in the first 3 days after the TIA were effectively excluded; a reanalysis of this study that accounted for the time with missing observations found that the 30-day stroke risk was 12% (Lovett et al., 2003), comparable to that seen in most other studies.

Regardless of the absolute value of the identified risk, the majority of studies have found that one-quarter to one-half of the strokes that occur within 3 months of the onset of TIA actually occur within the first 2 days (Johnston et al., 2000; Eliasziw et al., 2004; Gladstone

Table 23.2

Short-term stroke risk after TIA and after stroke

Study setting		Publication year	*n*	Delay (days)	Stroke risk	Projected 90-day stroke risk*
Transient ischemic attack						
Rochester, Minnesota (Whisnant et al., 1973)	Population-based cohort study	1973	198	0	10%/3 m	10%
London, UK (Humphrey and Marshall, 1981)	Cohort study	1981	117	0	29%/6 m	27%
Iowa City, Iowa (Putman and Adams, 1985)	Cohort study	1985	74	1	6.8%/6 d	13%
Iowa City, Iowa (Biller et al., 1989)	Pilot trial (placebo group)	1989	55	2	9.1%/6 d	16%
Oxfordshire, UK (Dennis et al., 1990; Lovett et al., 2003)	Population-based cohort study	1990	209	0	12%/1 m	15%
Northern California (Johnston et al., 2000)	Cohort study	2000	1707	0	10.6%/3 m	11%
Oxfordshire, UK (Coull et al., 2004)	Population-based cohort study	2004	87	0	17.3/3 m	17%
NASCET (Eliasziw et al., 2004)	Randomized trial (medical therapy)	2004	603	0	20.1%/3 m	20%
Nueces County, Texas (Lisabeth et al., 2004)	Prospective population-based study	2004	612	0	4.03%/3 m	4%
Alberta, Canada (Hill et al., 2004)	Population-based cohort study	2004	2285	1	9.5%/3 m	10%
Ontario, Canada (Gladstone et al., 2004)	Cohort study	2004	265	0	6%/3 m	6%
Southwest Germany (Daffertshofer et al., 2004)	Population-based cohort study	2004	1150	0	13%/6 m	11%
Greater Cincinnati/Northern Kentucky (Kleindorfer et al., 2005)	Population-based cohort study	2005	927	0	11.2%/1 m	15%
AVERAGE						11%
Ischemic stroke						
London, UK (Humphrey and Marshall, 1981)	Cohort study	1981	117	0	14%/6 m	12%
NINDS Stroke Data Bank (Sacco et al., 1989; Hier et al., 1991)	Cohort study	1989	1273	0	3.3%/1 m	4%
Oxfordshire, UK (Burn et al., 1994)	Population-based cohort study	1994	545	0	~8%/6 m	4%
Lehigh Valley, Pennsylvania (Lai et al., 1994)	Cohort study	1994	621	0	9%/12 m	4%
New York, New York (Sacco et al., 1994)	Population-based cohort study	1994	323	0	6%/1 m	7%

FISS (Kay et al., 1995)	Randomized trial (placebo)	1995	105	1	3.8%/3 m	4%
IST (International Stroke Trial Collaborative Group, 1997)	Randomized trial (aspirin/ placebo)	1997	9717	1	3.3%/2 w	7%
CAST (CAST Collaborative Group, 1997)	Randomized trial (placebo)	1997	10320	1	2.5%/1 m	6%
Perth, Australia (Hankey et al., 1998)	Population-based cohort study	1998	250	0	~7%/6 m	5%
TOAST (The Publications Committee for the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) Investigators, 1998)	Randomized trial (placebo)	1998	628	1	5.7%/3 m	6%
New York, New York (Moroney et al., 1998)	Cohort study	1998	297	0	7.4%/3 m	7%
Rochester, Minnesota (Petty et al., 1998)	Population-based cohort study	1998	1111	0	9%/6 m	7%
TAIST (Bath et al., 2001)	Randomized trial (aspirin)	2001	491	1	3.1%/5 d	8%
NASCET (Eliasziw et al., 2004)	Randomized trial (medical therapy)	2004	526	0	2.3%/3 m	2%
Oxfordshire, UK (Coull et al., 2004)	Population-based cohort study	2004	87	0	18.5/3 m	19%
Southwest Germany (Daffertshofer et al., 2004)	Population-based cohort study	2004	3038	0	13%/6 m	10%
AVERAGE						7%

*Projections were calculated by interpolating outside the period of study with the risk from Johnston, et al, for TIA and Petty, et al, for stroke since these studies were large and provided complete data on period risks. When 90-day risks were not provided directly, they were estimated from survival curves or by projection. Averages are weighted by study size; studies in which an estimate of 90-day risk is not available were not included. Reprinted from Johnston and Ruff (2005) with permission from Taylor & Francis.

et al., 2004; Hill et al., 2004; Lisabeth et al., 2004; Kleindorfer et al., 2005; Rothwell and Warlow, 2005). A retrospective analysis of the time between TIA and stroke revealed that stroke even occurs on the same day as the TIA in a substantial number of patients (Rothwell and Warlow, 2005), and studies in Oxfordshire and Northern California found the risk of stroke in the first 24 hours after TIA to be about 4% (Johnston et al., 2000; Lovett et al., 2003). For comparison, this is about twice the risk of myocardial infarction or death in patients presenting with acute coronary syndromes (about 2% at 24 hours) (Rao et al., 2003). These findings underscore the need for prompt evaluation and treatment of patients with symptoms of ischemia.

Completed stroke appears to carry a lower short-term risk of subsequent ischemic stroke than TIA, with reported 3-month risks generally ranging from 4% to 8% (Humphrey and Marshall, 1981; Sacco et al., 1989; Hier et al., 1991; Burn et al., 1994; Lai et al., 1994; Sacco et al., 1994; Kay et al., 1995; CAST Collaborative Group, 1997; International Stroke Trial Collaborative Group, 1997; Hankey et al., 1998; Moroney et al., 1998; Petty et al., 1998; The Publications Committee for the Trial of ORG 10172 in Acute Stroke Treatment [TOAST] Investigators, 1998; Bath et al., 2001; Coull et al., 2004; Daffertshofer et al., 2004; Eliasziw et al., 2004) (Table 23.2). As after TIA, the risk of recurrence appears to be greatest in the first few days. Studies finding higher rates of recurrent stroke have tended to use definitions that included clinical worsening without the requirement for imaging documentation; however, in the absence of imaging data it may be difficult to distinguish a new ischemic event from deterioration due to edema.

Six studies have directly compared the short-term risk of ischemic stroke following TIA and ischemic stroke. A small community-based study (Coull et al., 2004) found the risk of recurrent stroke within 3 months to be similarly high after TIA (17.3%) or minor stroke (National Institutes of Health Stroke Scale [NIHSS] ≤ 3; 18.5%). This differed from the other studies, which generally found TIA to impart a higher risk than completed stroke. In patients with hemispheric ischemia enrolled in the NASCET trial, the 90-day risk of stroke was 20.1% in the 603 with index TIA and 2.3% in the 526 with an index ischemic stroke (Eliasziw et al., 2004). Short-term risks were also greater after TIA than after ischemic stroke in a population-based study from Rochester, Minnesota (Wiebers et al., 1982), and in an observational study of consecutive patients with acute ischemic cerebrovascular events, which found the 6-month risk of recurrence to be 29% after TIA and 7% after completed stroke (Humphrey and Marshall, 1981). Finally, in two reanalyses of data from randomized trials, we found that the 90-day risk for subsequent neurological deterioration attributed to a cause other than new hemorrhage was two- to five-fold greater in those with complete recovery at 24 hours (that is, those with TIA) than in those with no recovery at 24 hours (Johnston and Easton, 2003; Johnston et al., 2003b).

23.5.2. Ischemic preconditioning/ischemic tolerance

Although TIA carries a high risk of subsequent stroke, it has been hypothesized that a preceding TIA can reduce the severity of a stroke. In animal models, an episode of ischemia can protect against infarction from a second ischemic event, presumably through the activation of cellular defense responses (Kirino, 2002). Several studies (Weih et al., 1999; Moncayo et al., 2000; Arboix et al., 2004; Sitzer et al., 2004; Wegener et al., 2004) have suggested that such ischemic preconditioning also occurs when the first ischemic insult is a TIA, resulting in subsequent strokes of reduced severity compared to those that are not preceded by a TIA. In contrast, in a recent analysis of data from the Northern California TIA study using the duration of the original TIA as a surrogate for the "dose" of ischemic preconditioning (Johnston, 2004), we did not find that TIA duration was associated with the likelihood that a subsequent stroke was disabling. Furthermore, there was no significant difference in the rate of disability between patients whose index TIA occurred 1–7 days before the stroke, the period when ischemic preconditioning would have been expected, and those whose strokes occurred outside of this period.

23.5.3. TIA as predictor of cardiac events

In addition to being a predictor of ischemic stroke, TIA can also be a warning of impending cardiac events. In the Northern California TIA study, 44 patients (2.6%) were hospitalized for cardiovascular events within 90 days. Although the short-term risk of a cardiac event is thus lower than that of stroke (90-day risk of $\sim$11%), over the course of 5 or more years nearly equal numbers of patients with TIA will have myocardial infarction or sudden cardiac death as will have a cerebral infarction (Heyman et al., 1984), and more patients with TIA will die of a cardiac event than of a completed stroke (Cartlidge et al., 1977; Heyman et al., 1984; Whisnant and Wiebers, 1987). ECG is recommended as part of the routine evaluation following a TIA (Feinberg et al., 1994), and several studies (Heyman et al., 1984; Pop et al., 1994; Elkins et al., 2002) have found that abnormal ECG findings after TIA identify patients at high risk

for an ischemic cardiac event even in patients with no history of heart disease (Elkins et al., 2002), and without a definite or probable cardio-embolic source of the cerebral ischemia (Pop et al., 1994). Elkins et al., (2002) found that TIA patients with any abnormal ECG finding had a 90-day risk of a cardiac event of 4.2%, compared to 0.6% in TIA patients without abnormal ECG and 0.39% in age-matched controls. Studies have disagreed whether abnormal ECG findings are (Pop et al., 1994) or are not (Elkins et al., 2002) also predictive of subsequent stroke.

23.5.4. Who is most at risk of stroke after TIA?

Approximately 5% of patients with TIA will have completed ischemic stroke within 2 days of the TIA (Johnston et al., 2000). The ability to identify those patients with the highest short-term risk would aid in directing resources to where they are most needed.

TIA-type and other clinical and demographic factors have been shown to predict outcome. Although transient monocular blindness (amaurosis fugax) is associated with a higher risk of hemispheric stroke than is found in the general population, this risk has consistently been found to be lower than that following hemispheric TIAs (Hurwitz et al., 1985; Wilterdink and Easton, 1992; Streifler et al., 1995; Benavente et al., 2001), and the strokes that do occur are often less disabling (Benavente et al., 2001). The presence of a new infarct on brain imaging is associated with an approximately two- to four-fold increase in risk (Douglas et al., 2003; Daffertshofer et al., 2004; Eliasziw et al., 2004; Purroy et al., 2004). The presence of an infarct may also reflect that the event truly had an ischemic cause and was not a TIA mimic.

Increases in the blood levels of a variety of chemicals, such as homocysteine (Bos et al., 2005) and fibrinogen (Rothwell et al., 2004b), have been correlated with increased risk of stroke in patients with TIA. Levels of fibrinogen, a major determinant of blood viscosity, are weakly but significantly associated with acute ischemic stroke patients with TIA and more strongly associated with acute coronary events (Rothwell et al., 2004b).

Several reports (Kernan et al., 1991; Johnston et al., 2000, 2003a; Hill et al., 2004; Rothwell et al., 2005) have used statistical analyses to develop profiles of risk factors. Five factors independently associated with stroke within 90 days of TIA were identified in the Northern California TIA study: age >60, diabetes mellitus, symptom duration > 10 minutes, weakness, and speech impairment (Johnston et al., 2000). The risk increased with the number of risk factors, up to a 90-day risk of ischemic stroke of 34% for patients with five risk factors. Similarly, a population-based study (Hill et al., 2004) found that the risk of stroke at 1 year was greatest among patients over 65 or with hypertension or diabetes mellitus, although these factors did not increase risk at 2 days or 30 days; the same factors have been shown to be risk factors for stroke or death within 2 years following a first carotid TIA or minor stroke (Kernan et al., 1991).

Data from the Northern California TIA study were also examined to determine which factors were more likely to be associated with recurrent TIA than with stroke (Johnston et al., 2003a). Patients with these factors may represent a population at lower risk. An age of over 60 was the only independent risk factor for both stroke and recurrent TIA. A history of multiple TIAs, duration of symptoms $\leq$10 minutes, and sensory abnormalities were all independent predictors of recurrent TIA rather than stroke.

A recent study (Rothwell et al., 2005) set out to derive a score to identify which patients need emergency assessment and which can be managed as outpatients. Of 209 patients with TIA in the Oxfordshire Community Stroke Project, 18 patients who had strokes within 7 days of the index TIA were examined for the presence or absence of the factors previously reported (Johnston et al., 2000; Hill et al., 2004) to be independent predictors for stroke over a longer period (3 months or 1 year): age (>60 or <60), clinical features (motor weakness and speech disturbance), duration of symptoms, diabetes, and hypertension. A six-point scale was developed and then validated in the OXVASC cohort of 399 patients with probable or definite TIA, 38 of whom had a stroke within 7 days. The risk of stroke within 7 days ranged from 0% in patients with a score <4 to 35.5% in patients with a score of 6.

The groups from Northern California and Oxford pooled their cohorts and developed a new score, the $ABCD^2$ score, meant to replace the prior California and ABCD scores. The score was developed in two cohorts and validated in four others, and was superior to prior scores, with excellent prediction of stroke risk at 2, 7, 30, and 90 days after TIA (Johnston 2006).

23.5.5. Rapid recovery as an indicator of risk

Some studies have suggested that there is no difference in risk of stroke between patients who have completely recovered at 24 hours (i.e. those who meet the current definition of TIA) and those who have substantial early recovery but still have mild residua beyond the 24-hour cut-off. In the Northern California TIA study, 181 patients had dramatic rapid recovery without documentation of complete resolution of symptoms within 24 hours (Johnston et al., 2000). The 90-day risk of stroke in this group was 10.4%, identical to that in the

group with complete resolution. Similarly, two separate analyses showed that those with >75% recovery on the NIHSS at 24 hours after presentation were more likely to deteriorate in the following 90 days (Johnston and Easton, 2003; Johnston et al., 2003b). Thus, it appears that complete recovery is not necessary to raise the risk of subsequent stroke. The important characteristic could therefore be either the degree of residual neurological impairment (i.e. impairment below a certain threshold increases the risk) or the amount that the patient improved over a short period of time, regardless of the residual deficit (Fig. 23.2). In patients with TIA, by definition, there is no residual impairment and rapid recovery of an ischemic deficit has occurred. Data from patients with acute ischemic stroke support the idea that rapid recovery rather than degree of residual impairment is the important predictor of subsequent ischemic stroke risk. Among 50 consecutive patients with rapid recovery from acute ischemic cerebrovascular events (defined as improvement to an NIHSS score <4 within 6 hours of symptom onset), 16% deteriorated within 24 hours (Alexandrov et al., 2000). Similarly, in the National Institutes of Neurological Disorders and Stroke tPA Trial, 12% of the 312 treated with placebo had rapid improvement followed by deterioration within 10 days (9% within 24 hours) (Grotta et al., 2001); over 70% of the deteriorations were attributed to reocclusion of the symptomatic artery. Another recent study showed that improvement in the 7 days after a completed ischemic stroke also predicts subsequent deterioration, with each 10% rise in recovery associated with a 16% increase in the risk of neurological deterioration as defined by a composite measure including worsening NIHSS score, recurrent stroke, or stroke-related adverse events (Aslanyan et al., 2004).

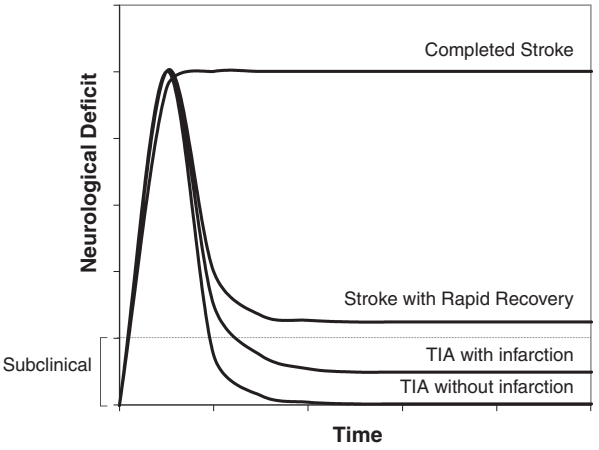

Fig. 23.2. Time courses of neurological impairment among hypothetical patients presenting with acute focal brain ischemia. Distinctions between stroke with ischemic recovery, transient ischemic attack (TIA) with infarction, and TIA without infarction may be less important than the distinction between these entities and completed stroke with no rapid recovery. Rapid recovery is likely to represent reversal of cerebral ischemia, and may be an indicator of instability; it may thus be a more important determinant of subsequent risk of stroke than whether the deficit completely resolves over a certain period.

The extent of early improvement after presentation with an acute ischemic cerebrovascular event may be associated with risk of subsequent stroke because rapid recovery may indicate a distinct, unstable pathophysiology in some instances (Alexandrov et al., 2000; Grotta et al., 2001). Rapid recovery is an indicator that previously ischemic territory has returned to normal function, perhaps due to lysis of a thrombus or the presence of collateral blood flow. However, the responsible plaque may remain highly thrombogenic, collateral flow may be inadequate to maintain compensation when the blood pressure is lower (Rordorf et al., 1997) or if there is brain swelling, or an embolism can recur, leaving the patient at high risk of a subsequent ischemic event. If a ruptured plaque leads to a completed stroke in the distal vascular territory, additional thrombosis will generally be asymptomatic; the situation is relatively stable and risk of a clinically apparent new stroke is low. Supporting this, a recent study in patients with ischemic stroke found imaging evidence of recurrent ischemia in 34% of patients during the first week after stroke, although the infarction was clinically evident in only 2% (Kang et al., 2003). The new ischemia in these patients may have been "silent" because the index stroke involved regions with similar function, thus masking the new infarction; the symptoms of new infarction may also be attributed to the deterioration commonly seen after stroke. Recurrent ischemia would be expected to be clinically apparent more frequently after rapid recovery, a situation in which new infarction occurs on the "clean slate" of normal or minimally impaired neurological function. Patients with rapid recovery may therefore benefit the most from aggressive antithrombotic therapy, neuroprotective agents, and interventions (such as pressors or fluids) that increase collateral blood flow; however, this needs to be tested in prospective clinical studies.

23.6. Management and stroke prevention

23.6.1. How urgently should patients with TIA be evaluated and treated?

Given the high risk of subsequent stroke in patients with TIA and in those with rapid recovery without complete resolution, this group may need to be treated

with particular urgency. Whether or not to hospitalize these patients for evaluation and treatment has been a matter of debate. Hospitalization is expensive (Gubitz et al., 1999), and for the majority of patients, urgent outpatient evaluation would be sufficient. A retrospective study found that many hospitalizations for TIA and stroke were not medically justified; however, about half that were justified based on outcome would not have been deemed so in the emergency department (Henneman and Lewis, 1995), and it may be better to err on the side of caution. Hospital admission is associated with a decreased risk of stroke (Hill et al., 2004), and the short-term costs of hospitalization for TIA may result in long-term cost savings if a stroke is prevented or if tPA is more likely to be administered if a stroke occurs (Nguyen-Huynh and Johnston, 2005). Progress in identifying those most at risk of a subsequent stroke will help to balance the need for hospitalization and urgent treatment in those at high risk with the need to reduce costs.

Most patients presenting with symptoms suggestive of a TIA should be evaluated in an emergency department immediately, and hospitalization is generally indicated if the patient is at high risk or if there will be a delay of more than 24 hours in completing the initial evaluation (Henneman and Lewis, 1995; Johnston, 2002; Franklin et al., 2004). A report from the American Academy of Neurology recommends hospitalization for any patient with TIA within the previous 48 hours, particularly TIA of more than 30-minutes duration; frequent TIA; or symptoms suggestive of severe, treatable vascular occlusion (Lanska, 1994). Note, however, that others have found that repeated TIA does not increase the risk of stroke (Johnston et al., 2003a). Experience in the United Kingdom indicates that many patients will have a completed stroke before their appointment at an outpatient stroke clinic (Rothwell et al., 2005; Widjaja et al., 2005), and these clinics are therefore unlikely to be effective in preventing stroke unless patients can be seen the same day. It is also worth considering that patients whose symptoms have resolved may not appreciate the urgent need for evaluation and treatment and may fail to follow through with an outpatient evaluation (Franklin et al., 2004).

23.6.2. Prevention of secondary ischemic events

Because, by definition, TIA does not lead to lasting impairment, its management focuses on reducing the risk of subsequent events and may include a combination of surgery, medical management, and lifestyle changes, based on the probable source of ischemia and the patient's history. Many of these preventive measures are the same as those used for secondary prophylaxis following completed stroke. Indeed, many trials of therapies have included both patients with ischemic stroke and with TIA, with the assumption that response to secondary prevention will be similar in these groups. However, few studies have tested therapies exclusively in patients with TIA, and clinical trials specifically aimed at this population would greatly aid in management decisions.

The American Heart Association (Feinberg et al., 1994; Albers et al., 1999; Wolf et al., 1999) and the National Stroke Association (Brott et al., 2000) have published guidelines for the evaluation and management of TIA (Table 23.1). However, these guidelines tend to be vague and are slightly outdated. Actual practice varies considerably (Johnston and Smith, 1999), and recommended therapies are often underused (Goldstein et al., 2000; Gibbs et al., 2001; Saitto et al., 2004; Volpato et al., 2004).

23.6.2.1. Carotid endarterectomy

Carotid endarterectomy, the current standard of care for severe carotid stenosis, has been shown to reduce subsequent stroke when the carotid artery is >70% stenosed (North American Symptomatic Carotid Endarterectomy Trial Collaborators, 1991; Barnett et al., 1995; Sacco, 2001), but the benefits of endarterectomy are less clear for less extensive stenosis: endarterectomy results in only a small reduction in subsequent stroke for patients with 50–69% stenosis, and the risks of the surgery may outweigh the benefits in some cases (Barnett et al., 1998; European Carotid Surgery Trialists' Collaborative Group, 1998). Endarterectomy provides no benefit over medical therapy for those with less than 50% stenosis (Barnett et al., 1998). It is unknown whether the benefits of urgent surgery—a reduction in the short-term risk of stroke—outweigh the potential risks due to unstable plaque or acute thrombus; however, pooled data from North American and European trials suggests that those undergoing endarterectomy within 2 weeks are more likely to benefit than those treated later (Rothwell et al., 2004a). The surgery should probably be performed as soon as possible unless there is extensive brain infarction; there is little evidence to support delaying endarterectomy for more than 6 weeks to reduce the risk of brain hemorrhage (Mead et al., 1997; Biller et al., 1998). Stenting may also be an option in patients at high risk for surgery (Brott et al., 2004).

23.6.2.2. Medical therapies

Antiplatelet agents and anticoagulants have an important role in stroke prevention after TIA (Matchar et al., 1994; Elkind, 2004). Both antiplatelet agents

and anticoagulants elevate the risk of brain hemorrhage, thereby reducing their benefit following acute stroke. Although the risk may be lower after TIA, because there is a lower risk of hemorrhage with less severe ischemic events (The Publications Committee for the Trial of ORG 10172 in Acute Stroke Treatment [TOAST] Investigators, 1998), this has not yet been tested.

Aspirin, clopidogrel, and a dipyridamole/aspirin combination are all treatment choices for the secondary prevention of stroke, although no data specific to TIA are available. Which to choose continues to be vigorously debated (Dutch TIA Trial Study Group, 1991; Antiplatelet Trialists' Collaboration, 1994; Matchar et al., 1994; CAST Collaborative Group, 1997; International Stroke Trial Collaborative Group, 1997; Albers et al., 1999; Chen et al., 2000; Diener et al., 2004; Tran and Anand, 2004) and is currently being tested in trials such as PRoFESS (Prevention Regimen For Effectively avoiding Second Strokes) (Sacco et al., 2004). Ticlopidine is only rarely used because of concerns about safety.

Anticoagulation is indicated for patients with cardiac sources of emboli, particularly atrial fibrillation. Warfarin has been shown to be effective in reducing the risk of stroke in patients with atrial fibrillation (Ezekowitz and Levine, 1999; Hart et al., 2004; Saxena and Koudstaal, 2004; Tentschert et al., 2004). The benefits of heparin have not been shown to exceed the risks in most studies (Kay et al., 1995; The Publications Committee for the Trial of ORG 10172 in Acute Stroke Treatment [TOAST] Investigators, 1998; Berge et al., 2000; Saxena et al., 2001; Hart and Easton, 2002; Tentschert et al., 2004), but because the risks of hemorrhage may be lower in patients with TIA and the risk of recurrent ischemia remains high, urgent anticoagulation in those with atrial fibrillation and TIA is reasonable. However, further study will be required to obtain a definitive answer.

23.6.2.3. Modification of risk factors

Interventions that are known to reduce cardiovascular risk may also be effective in the prevention of cerebrovascular events. Long-term prevention of stroke may therefore require addressing known risk factors (Wolf et al., 1999). Studies of statin efficacy, while rarely focused on stroke prevention, have found a relative reduction in stroke of 20–25% in high-risk patients (Anonymous, 2004). Statins may reduce the risk of cardiac events by stabilizing atherosclerotic plaques (Maron et al., 2000), and may therefore have particular use in reducing the risk of subsequent cerebral ischemia after rapid recovery from an initial ischemic event. Ongoing treatment with statins may also reduce the severity of strokes, particularly in patients with diabetes (Greisenegger et al., 2004). Similarly, a number of trials have shown that reduction of blood pressure in subjects with risk factors such as coronary heart disease and diabetes reduces the incidence of stroke (Hilleman and Lucas, 2004), although some antihypertensives, notably ACE inhibitors, may have benefits through mechanisms other than reducing blood pressure (Hilleman and Lucas, 2004). Lowering blood pressure and cholesterol appears to reduce the risk of stroke even in patients with "normal" levels (Johnston, 2002; Muir, 2004), suggesting that most patients would benefit from treatment with antihypertensives and statins. Diabetes is a major risk factor for stroke following TIA (Johnston et al., 2000; Hill et al., 2004), and impaired glucose tolerance is frequently identified following a TIA or nondisabling stroke, even in patients not previously diagnosed with this condition (Kernan et al., 2005). In patients with coronary heart disease, both elevated and very low glucose levels are associated with increased risk of stroke or TIA (Tanne et al., 2004). Control of blood glucose may therefore lower the risk of stroke, and antihyperglycemic therapies should be tested for their effectiveness in preventing stroke (Kernan et al., 2005). No studies have specifically evaluated the benefit of lifestyle changes after TIA, but observational studies suggest that smoking cessation, exercise, weight control, and moderate alcohol consumption may reduce the risk of stroke (Feinberg et al., 1994), in part by reducing risk factors such as hypertension and diabetes.

23.7. Conclusions

TIAs are common and, although commonly viewed by the public as benign, are frequently precursors to severe cerebrovascular and cardiovascular events and should be viewed as an opportunity for intervention. To this end, the public must be made aware of the need to seek medical care even for symptoms that resolve quickly, and treating physicians need to make better use of the available therapeutic options.

The distinction between TIA and stroke is increasingly an artificial one: an acute infarction is present in a large number of patients with the clinical symptoms of TIA, and the risk of subsequent events is high in patients with rapid recovery even if that recovery is incomplete at 1 hour or 24 hours. Indeed, rapid recovery appears to be an important indicator of unstable pathophysiology and tissue at risk, and the very high short-term risk of subsequent events may justify the use of aggressive therapies in these patients, although most therapies have yet to be evaluated in trials of patients with TIA. Rather than shifting the line between TIA

and stroke, it may be time to replace these terms altogether with a more comprehensive functional term, such as "acute cerebrovascular ischemic event," qualified by the degree of rapid recovery, presence of infarct, severity, duration, or other relevant factors that will have the greatest impact on prevention of future ischemic events.

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Chapter 24

Medical complications of stroke

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Stroke patients are prone to develop complications as a result of the stroke and the disability caused by it. Complications after stroke may be caused by pre-existing medical conditions, such as atherosclerosis, prolonged bed rest and immobility, iatrogenic interventions, stroke-related therapeutics, or they may be a direct consequence of the stroke itself. A variety of medical and neurological conditions can occur, many of which can prolong the length of hospital stay and impede neurological recovery. Although several studies on medical complications in stroke patients have been published, the frequency of medical complications among patients with stroke during their inpatient stay is difficult to ascertain due to inter-study variations in the criteria used to define complications, the nature of the study (retrospective versus prospective), the duration of follow-up, and the patient population. Overall, the reported figures range from 48% to 96%. In one study, three of every four stroke patients experienced a complication during their hospitalization, and many had more than one medical condition (Roth et al., 2001).

The occurrence of complications after stroke is facilitated by several factors, such as advanced age, pre-stroke disability, pre-existing medical conditions, low serum albumin level, and increasing length of hospital stay. However, the severity of neurological deficits resulting from the stroke plays a dominant role. The likelihood and number of complications often correlate with stroke severity, and patients with the most severe neurological impairments tend to experience the most serious complications.

The incidence of medical complications after stroke has a significant impact on the cost of stroke care and patient's outcome. Some of these complications can be serious, life threatening, or fatal. Approximately 50% of all in-hospital deaths after stroke are attributed to medical or neurological complications (Heuschmann et al., 2004). It is, therefore, important to anticipate and prevent these complications in order to optimize the outcome of stroke survivors and to facilitate recovery. Most post-stroke complications are potentially preventable and treatable. Rapid recognition and management of these conditions can have a significantly positive impact on stroke-related morbidity and mortality.

24.1. Neurological complications

24.1.1. Increased intracranial pressure

Increased intracranial pressure (ICP) after stroke results from brain edema and secondary mass effect. Although brain edema may begin within hours of stroke onset, symptomatic increase in ICP usually develops 2–4 days afterwards. The severity of brain swelling also depends on stroke size and location. Large posterior fossa and malignant middle cerebral artery infarcts, especially in younger patients, are more likely to be ominous. Increased ICP after stroke occurs in 2–6% of patients. It is, by far, the complication with the highest attributable risk proportion for in-hospital mortality after stroke. In a large study compiling data from 104 German hospitals, 94% of stroke patients who developed increased ICP died during hospitalization, accounting for 29% of all stroke-related in-hospital mortality (Heuschmann et al., 2004).

Increased ICP may manifest as headache, drowsiness, or vomiting. Examination may reveal papilledema, sixth nerve palsies, periodic breathing, pupillary asymmetry, development of contralateral hemispheric signs, or signs of upper brainstem compression. Signs of uncal herniation need not always be present to suspect

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increased ICP in patients with stroke. Head CT or MRI may show evidence of peri-infarct edema, mass effect, midline shift, compression of the ventricles, or obstructive hydrocephalus (in case of posterior fossa infarcts).

Therapeutic measures to decrease ICP include: (1) head of bed elevation; (2) avoiding hypotonic solutions and overhydration, as they may aggravate cerebral edema; (3) control of pain and agitation with opioids or benzodiazepines; (4) osmotic diuresis with mannitol or hypertonic saline; (5) high-dose barbiturates; and/or (6) hypothermia. Hyperventilation to induce hypocapnia (pCO_2 25–30 mmHg) may be used to temporarily decrease ICP. Placement of an intraventricular shunt to drain cerebrospinal fluid may be required if hydrocephalus develops. Surgical decompression to remove an infarct (especially in the cerebellum) or to drain a hematoma can be life saving in some circumstances. Similarly, hemicraniectomy may be considered in young patients with large hemispheric infarcts and incipient herniation.

24.1.2. Seizures

Seizures may occur at stroke onset, or after stroke. The incidence of seizures after stroke varies from 6% to 10% in various studies. Thirty to fifty percent of seizures following stroke occur within the first 2 weeks of stroke onset, predominantly within the first 2 days. These early seizures are often isolated events, and are thought to result from acute metabolic changes in the brain after stroke. Patients with hemorrhagic strokes and cortical infarcts of cardioembolic origin are at the highest risk for early seizures, and those with large cortical infarcts are most susceptible to develop epilepsy. Early seizures are usually focal with secondary generalization, and may cause worsening of neurological deficits.

Some electroencephalographic features can be of predictive value concerning the likelihood of developing seizures after stroke. Patients with periodic lateralizing epileptiform discharges or focal spikes may be at increased risk. Post-stroke seizures usually respond well to treatment with anti-epileptic drugs. Prophylactic therapy is unnecessary, except for patients with subarachnoid or large parenchymal hemorrhages.

24.1.3. Stroke recurrence or progression

Worsening neurological deficits develop in more than 25% of stroke patients, mostly within the first 72 hours. Neurological deterioration is often secondary to increased ICP, seizures, or more commonly a host of medical complications such as pneumonia and urinary tract infections. Deterioration in patients with brain hemorrhage is usually the result of continued bleeding, re-bleeding, and increased ICP. Re-bleeding, vasospasm with subsequent ischemia, development of hydrocephalus, and hyponatremia are often associated with worsening neurological status in patients with subarachnoid hemorrhage.

Progression of ischemic strokes is less common, and is usually encountered in patients with large-vessel occlusion or high-grade stenosis, or lacunar infarcts. It is usually attributed to propagation of thrombi, embolism, decrease brain perfusion as a result of a drop in blood pressure, and inadequate collateral circulation.

The complication rate of recurrent stroke during hospitalization varies from 2.5% to 7.6% (Weimar et al., 2002). The risk of stroke recurrence is 0.1% to 1% per day during the first 14 days after the stroke (Saxena et al., 2001). The likelihood of stroke recurrence depends on the mechanism of the first stroke and treatment. Patients with atrial fibrillation (AF) are more likely to suffer a fatal recurrent event than those without AF (Saxena et al., 2001).

Treatment depends on stroke type, mechanism, and underlying cause of neurological deterioration. It is, therefore, cause-specific. Avoiding hypotension and dehydration to optimize cerebral perfusion pressure during the acute stage of ischemic stroke is recommended. The use of aspirin reduces the risk of recurrent ischemic stroke in the first 2 weeks by 30% (Saxena et al., 2001).

24.1.4. Cerebral hemorrhage secondary to thrombolytic or anticoagulant therapy

Intracerebral hemorrhage (ICH) is a potentially lethal complication of tissue plasminogen activator (rt-PA) therapy for ischemic stroke. The rate of ICH associated with deterioration of neurological status after intravenous thrombolysis with rt-PA in the National Institute of Neurological Disorders and Stroke (NINDS) study was 6.4% (National Institute of Neurological Disorders and Stroke rt-PA Study Group, 1995). Most of these hemorrhages occurred within 24 hours of the patients receiving rt-PA, and almost half of these patients died. Higher rates of ICH (7–9%) were reported in the European Cooperative Acute Stroke Study (ECASS) II and Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) trials, which used a 6-hour window for intravenous rt-PA administration (Hacke et al., 1995; Clark et al., 1999). A number of studies indicate that advancing age, elevated blood pressure, high serum glucose level, increased white cell count, increasing severity of pretreatment deficits, extensive ischemic changes seen on CT scan, and embolic occlusion of the

M1 segment of the middle cerebral artery are associated with higher risk for ICH after treatment with rt-PA. Some studies suggest that the detection of cerebral microbleeds on T2*-weighted imaging gradient echo MRI may be indicative of a higher risk for symptomatic ICH after thrombolytic or other antithrombotic therapies. However, the data are inconsistent.

Adherence to current guidelines for thrombolysis in patients with acute ischemic stroke and maintaining a blood pressure less than 185/105 mmHg may help to reduce the incidence of secondary ICH. Close monitoring of stroke patients who receive thrombolytic or anticoagulant therapy, and rapid brain imaging at the earliest signs of neurological deterioration allows rapid detection of secondary ICH. Treatment is supportive. Transfusion with platelets, fibrinogen, and cryoprecipitate is often undertaken. Surgical evacuation or decompression may be considered in some cases.

24.2. Medical complications

24.2.1. Venous thromboembolism

Systemic venous thrombotic complications occur in as many as 50% of patients during the first 2 weeks of stroke. However, most cases are clinically silent and often go undetected. Immobility, degree of hemiplegia, and severity of the acute illness are predisposing factors for venous thrombosis. Patients with congestive heart failure may be at increased risk.

24.2.2. Deep venous thrombosis

The incidence of deep venous thrombosis (DVT) peaks at 7 days after stroke onset, but it may occur as early as the second day. The risk for DVT may be as high as 7% on the nonparetic side compared with 75% in the paretic side. Diagnosis can be easily confirmed by duplex scanning.

24.2.3. Pulmonary embolism

Pulmonary embolism (PE) is potentially fatal. It usually occurs in stroke patients who have DVT in lower extremities or pelvic structures, and its incidence peaks at 2–4 weeks after stroke onset. In one study, 93% of stroke patients who developed PE died in hospital, accounting for 4% of all stroke-related in-hospital mortality (Heuschmann et al., 2004).

Clinically, PE may manifest as dyspnea, chest pain, shortness of breath or a change in respiratory pattern, hypotension, and agitation or confusion. Examination may reveal fever, tachycardia, tachypnea, hypoxemia, accentuated second heart sound, or rales. A high index of suspicion is essential for early diagnosis and treatment. Nuclear scintigraphic ventilation–perfusion (V/Q) scanning of the lung is the single most important diagnostic modality for detecting PE. It is indicated whenever the diagnosis of PE is suspected and no alternative diagnosis can be proved. Pulmonary angiography remains the standard for the diagnosis of PE, with a positive predictive value of 100% and a negative predictive value greater than 90%.

Prevention is of paramount importance. Early ambulation and bedside physical therapy are recommended. Prophylaxis with unfractionated heparin (5000 units injected subcutaneously every 12 hours) or low-molecular-weight heparin (30 mg subcutaneously every 12 hours), and/or pneumatic compression boots is recommended for nonambulatory stroke patients. If DVT is detected or PE is seriously suspected, early heparin anticoagulation is advised. Anticoagulation should not wait for the results of diagnostic tests since PE may progress rapidly. Clearly, the risk versus benefit of anticoagulation, especially in the setting of a large infarct or ICH, should be weighted against the risks of venous clot propagation. Oxygen should be administered to every patient with suspected PE. Fibrinolytic therapy is the standard of care for all patients with massive or unstable PE, unless overwhelming contraindications exist. The overall risk of fatal ICH in stroke patients with PE who receive thrombolytic therapy is unknown, but is likely to be significantly higher than 2% (Dalen et al., 1997). Embolectomy and placement of a Greenfield filter in the inferior vena cava may provide alternatives in high-risk patients.

24.2.4. Cardiovascular complications

Heart disease is a leading cause of death after stroke. The prevalence of cardiovascular disease among stroke patients is high. Approximately three-quarters of stroke survivors have a cardiovascular disease, including hypertension, coronary artery disease and congestive heart failure. Early recognition and management of these conditions after stroke can reduce the morbidity and improve outcome of stroke patients.

24.2.4.1. Arrhythmias

A variety of electrocardiographic (ECG) changes occur in acute stroke patients, which cannot be fully attributed to the higher prevalence of concurrent cardiac disease among stroke patients. There appears to be a cause–effect relationship between the stroke and these ECG abnormalities. In one study, 77% of stroke patients who did not have any history of pre-existing cardiac disease had an abnormal ECG at one time during the first 7 days of stroke onset (Khechinashvili and

Asplund, 2002). In other studies, 33–50% of stroke patients had abnormal ECG rhythms, compared to 15–20% of controls matched for age and previous history of cardiac disease. Abnormal ECG findings in stroke patients include ST changes, prolonged QTc interval, bundle branch block, premature atrial and ventricular contractions, tachycardia, and bradycardia. Atrial fibrillation may also develop as a sequel to stroke. Asystole, complete atrioventricular block, or ventricular tachycardia, may occur, and can be potentially fatal. Sudden death occurs in approximately 1% of patients within the first month of stroke onset (Cheung and Hachinski, 2000). The ECG changes seen after strokes are thought to be secondary to sympathovagal imbalance resulting from involvement of brain regions that make up the autonomic descending system. The stress of stroke may also stimulate the release of catecholamines from the adrenal medulla and subsequent sympathetic predominance (Tokgozoglu et al., 1999).

Strokes involving the insular cortex, hypothalamus, and brainstem are more likely to be associated with ECG changes. Serious arrhythmias occur more frequently with hemispheric infarcts than brainstem infarcts. There may also be a differential impact of stroke laterality on cardiac rhythm. For example, strokes that involve the left insular cortex may be associated with tachycardia and increased blood pressure, whereas involvement of the right insula may cause bradycardia, prolonged QTc, and hypotension, and may be implicated in sudden death after stroke (Tokgozoglu et al., 1999; Cheung and Hachinski, 2000). Therefore, cardiac monitoring is advised in the immediate post-stroke period. Antiarrhythmic drugs and beta-blockers may be required in some cases. Cardioversion and pacemaker implantation are reserved for patients with significant hemodynamic instability.

24.2.4.2. Elevated cardiac enzymes

Creatine kinase may be elevated during the first few days after stroke onset. Similarly, cardiac troponin may be detected in up to one-third of acute stroke patients (Christensen et al., 2004). In one study, N-terminal pro-brain natriuretic peptide (NT-proBNP) levels were found to be elevated in 65% of patients with acute ischemic stroke (Etgen et al., 2005). The raised concentrations of cardiac enzymes during the early days after stroke may be secondary to primary myocardial damage that caused the stroke. However, it is not uncommon to find no clinical evidence of concurrent myocardial ischemia in stroke patients with elevated cardiac enzymes. Postmortem studies show that stroke patients have subendocardial hemorrhages and focal necrosis of the cardiac muscles (Connor, 1970). These changes may be secondary to sympathetic activation and release of catecholamines after stroke, which in turn result in elevated levels of biochemical markers of cardiac cell damage. Elevations of cardiac enzymes, as a result of stroke, tend to be longer lasting than those associated with a primary cardiac disease, peaking at day 5 and persisting until day 12 (Norris et al., 1979).

There are discordant reports of the possible impact of enzyme elevation on patient outcome. In one observational study, raised serum concentration of cardiac troponin was associated with a three-fold increase in mortality among patients with acute ischemic stroke (James et al., 2000). In contrast, a more recent prospective study in 147 consecutive patients with MRI-confirmed ischemic stroke found that neither cardiac troponins nor NT-proBNP influence clinical outcome when other risk factors are considered (Etgen et al., 2005).

24.2.4.3. Myocardial infarction

Myocardial infarction (MI) and angina occur in approximately 6% of patients with acute stroke. Sympathetic activation, which accompanies most strokes, may precipitate angina and MI. Myocardial infarction is a common cause of death during the first few weeks of stroke. Therefore, all stroke patients should be carefully monitored and questioned for signs and symptoms of myocardial ischemia, such as dyspnea on exertion, lightheadedness or a decrease in heart rate or blood pressure during exercise.

The treatment options for acute MI in patients with acute ischemic stroke may be limited. Thrombolytic or anticoagulant therapy may be contraindicated in the presence of a large infarct or ICH. Coronary angioplasty with or without stenting often requires concurrent use of heparin and IIb-IIIa inhibitors, and long-term use of aspirin and clopidogrel, a combination that increases the risk of ICH (Diener et al., 2004). Agents that reduce blood pressure (BP) must be used cautiously in patients with acute ischemic stroke and concomitant MI to avoid abrupt lowering of BP and subsequent decrease in cerebral perfusion.

24.2.5. Pulmonary complications

24.2.5.1. Oxygen desaturation and obstructive sleep apnea

The occurrence of oxygen desaturation in stroke patients is not uncommon. Stroke patients are at risk of hypoxia through alterations in the central regulation of respiration, through aspiration, and through respiratory muscle weakness. Stroke patients with severe deficits,

dysphagia, and cardiac or pulmonary disease are particularly at risk. Most cases are asymptomatic. However, sleep-related breathing disorders may lead to episodes of nocturnal hypoxia even when daytime oxygenation is normal. Obstructive sleep apnea (OSA) is detected in 60–90% of stroke patients (Brown et al., 2005) and its presence is associated with increased post-stroke morbidity and mortality. In one study, oxygen saturation in stroke patients at night was approximately 1% lower than when awake, and almost 25% of patients who had normal oxygen saturation during the day spent 30 minutes or more with an oxygen saturation <90% at night (Roffe et al., 2003). However, it is unclear if screening for OSA and treatment with continuous positive airway pressure (CPAP) improves neurological outcome in stroke patients. It is recommended that oxygen saturation after acute stroke should be maintained at 95% or higher.

24.2.5.2. Dysphagia and aspiration

Dysphagia and aspiration are common after stroke, and can be detected in up to 50% of patients on bedside testing (Mann et al., 2000). However, bedside testing for swallowing difficulties is suboptimal, since aspiration can be silent in a large number of stroke patients. Evidence of swallowing dysfunction is seen in as many as 60% of stroke patients when video fluoroscopy is used (Mann et al., 2000). Older age, stroke severity, impaired pharyngeal response, and palatal weakness are all predictors of dysphagia (Mann and Hankey, 2001). The absence of a gag reflex is of poor predictive value. Patients with bilateral hemispheric or brainstem strokes, and those with bulbar dysfunction are at higher risk for aspiration. Dysphagia and subsequent aspiration are risk factors for developing aspiration pneumonia. In a study of 114 stroke patients, the relative risk for developing pneumonia was seven times greater in patients who aspirated silently compared to those who coughed when aspirating or who did not aspirate (Holas et al., 1994). The risk for developing pneumonia is also greater for aspirating thick liquids or solids than for thin liquids. Fortunately, more than two-thirds of patients with dysphagia recover their swallowing abilities within weeks to months following their stroke, allowing safe oral feeding.

Early detection of swallowing difficulties and prevention of aspiration in stroke patients are key. Preventive strategies for patients at increased risk for aspiration may include: initial nil per os (NPO) status; modification of food consistency; upright position during feeding; and educating patients with regard to food positioning within the oral cavity. Swallowing evaluation by trained personnel is important in every stroke patient. Modified video fluoroscopic swallow studies are helpful for prescribing a safe diet.

24.2.5.3. Pneumonia

Pneumonia is the most common medical complications following stroke. It is also the complication with the highest attributable proportion of death in stroke patients, accounting for 31% of all stroke-related deaths in hospital (Heuschmann et al., 2004), and is the most common cause of fever in stroke patients within the first 2 days of stroke onset (Grau et al., 1999). It often results in prolonged hospitalization delaying the initiation of rehabilitation. Pneumonia in stroke patients is often multi-factorial, as a result of decreased mobilization of secretions in a recumbent position, atelectasis, dysphagia and aspiration of colonized oropharyngeal material.

Careful swallowing evaluation prior to initiation of oral feeding can prevent aspiration pneumonia. Treatment should include maintenance of airways and clearance of secretions with tracheal suctioning and oxygen supplementation. Early prophylactic use of antibiotics is controversial because no evidence indicates that bacterial infection, which often relates to chemical pneumonitis, plays a role in the initial stage. Antibiotics are the mainstay of treatment for bacterial pneumonia. The choice of antibiotics and duration of treatment depend on the suspected or proven causative organisms. Gram-negative organisms, including *Pseudomonas*, are commonly seen in hospital-acquired aspiration pneumonias. Therefore, gram-negative coverage with a third-generation cephalosporin or fluoroquinolone is often recommended. Antibiotic coverage for anaerobes may also be considered in patients with foul sputum, alcoholism, or severe periodontal disease.

24.2.5.4. Pulmonary edema

Acute pulmonary edema may develop after stroke, particularly subarachnoid hemorrhage. While it is tempting to invoke neurogenic pulmonary edema as the cause of pulmonary edema in stroke patients, the pathogenesis of pulmonary edema after stroke is mostly speculative. Neurogenic pulmonary edema is hypothetically attributed to sudden and severe increase in ICP, which causes massive sympathetic stimulation. However, a large percentage of patients with so-called neurogenic pulmonary edema are also found to have a depressed ejection fraction, suggesting that pulmonary edema is likely secondary to congestive heart failure (McLaughlin et al., 2005). Sudden onset of dyspnea is the most common symptom of pulmonary edema. Examination often reveals tachypnea, tachycardia, bibasilar crackles, respiratory distress, pulmonary edema with normal jugular venous pressure, and the absence of cardiac gallop.

The so-called “neurogenic pulmonary edema” is often self-limited, and usually resolves within 48–72 hours. Treatment is supportive. Supplemental oxygen

is required in most patients to correct hypoxemia. Mechanical ventilation may be necessary. Diuretic therapy may be used to minimize or reduce fluid overload, but adequate cardiac output and cerebral perfusion pressure must be maintained.

24.2.6. Genitourinary complications

24.2.6.1. Voiding dysfunction

Voiding dysfunction is common after stroke. Urinary frequency, urgency, and urge incontinence may occur in stroke patients, as a result of loss of inhibitory input from higher neurological centers causing detrusor hyperreflexia (Burney et al., 1996a). These symptoms are particularly common following frontoparietal and internal capsule infarcts and strokes above the pontine micturation center, which result in inhibition of normal reflex voiding. Communication impairment, perceptual deficits, and poor mobility from the stroke may also contribute to incontinence. Urinary incontinence tends to improve with time after stroke. Between 32–79% of stroke patients on admission, 25–28% on discharge, 20% at 3 months, 8% at 12 months and 3% at 2 years experience incontinence. The occurrence of incontinence after stroke is a poor prognostic sign. In one study that assessed stroke outcome, urinary incontinence was associated with increased mortality and disability at 2 years (Patel et al., 2001).

Detrusor hyporeflexia or areflexia may also occur after stroke, especially ICH, leading to urinary retention and occasionally overflow incontinence. In one study, urinary retention secondary to detrusor areflexia was seen in 85% of hemorrhagic infarcts, compared to only 10% of ischemic infarcts (Burney et al., 1996b).

Impaired consciousness, immobility, fecal impaction, use of anticholinergic drugs, and co-morbid diabetic cystopathy or bladder outlet obstruction may also contribute to urinary retention in stroke patients. Strokes involving various areas, including the frontoparietal region, internal capsule, basal ganglia, thalamus, pons and cerebellum, may be associated with detrusor areflexia and retention.

Evaluating urinary symptoms in stroke patients may be complicated by other co-morbidities, such as diabetes, cognitive impairment, or benign prostatic hypertrophy. Urinary symptoms can be easily overlooked if the patient is not directly queried. The treatment of detrusor hyper-reflexia includes scheduled timed voiding every 2–3 hours, fluid restriction, and anticholinergic drugs. Actively screening for urinary retention with routine measurement of post-void residual urine, and institution of corrective measures is important to prevent urinary tract infections (UTIs). The use of a Foley catheter should be discouraged to decrease the risk of nosocomial infections. Intermittent catheterization using sterile techniques is preferable if catheterization is required to empty the bladder.

24.2.6.2. Urinary tract infections

Urinary tract infections (UTIs) are frequent after stroke. In one study, UTIs occurred in 11% of stroke patients, but were only serious in 1% of cases (Roth et al., 2001). The high frequency of UTIs in stroke patients is attributed to the use of indwelling catheters and voiding difficulties caused by the stroke. The duration of catheterization relates to the risk of developing UTIs. It is, therefore, important to avoid the placement of a continuous catheter and to correct voiding difficulties to minimize the risk of UTIs. Catheter-related UTIs are usually caused by *Escherichia coli*. Polymicrobial infections and Enterococci are less common. The degree of leukocytosis and pyuria does not always correlate with the level of bacteruria. Urine cultures are important to confirm the diagnosis and treatment should be based on the culture results and sensitivities.

24.2.6.3. Sexual dysfunction

Sexual difficulties are not uncommon in stroke survivors. Men often report decreased libido, ejaculatory dysfunction, and less commonly, impotence. In women, decreased vaginal lubrication usually predominates. The changes in sexual function after stroke are multifactorial, and are attributed to emotional fear of stroke recurrence, post-stroke depression, physical disability caused by the stroke, medication effects (particularly antihypertensive agents such as beta blockers), genitourinary problems, or sensory and perceptual deficits. The treatment should involve coordinated physical, psychological, and sexual counseling approach. Sildenafil, and other similar drugs used for treatment of erectile dysfunction, should be used cautiously after a thorough cardiovascular evaluation. The use of vaginal estrogen replacement in women may be considered.

24.2.7. Psychological complications

24.2.7.1. Depression

Depression occurs in up to 60% of patients after stroke, and is attributed to the direct neuropsychological effects of the stroke itself, in addition to a reactive component related to the degree of disability. Women, young patients, patients with severe disability, and those with pre-stroke depression are at higher risk (Carota et al., 2005). Some studies suggest that anterior circulation and left hemispheric strokes result in greater frequency of depression compared to posterior circulation and right hemispheric stroke (Spalletta et al., 2002). However, this

is controversial. Dependency and lack of social contacts and support are important factors in chronic or late post-stroke depression. Post-stroke depression can have a negative impact on outcome, by decreasing motivation and magnifying existing disability. Depression at 3 months is correlated with poor outcome at 1 year and higher mortality. However, improvement in post-stroke depression does not always result in improvement of functional status.

The diagnosis of depression in stroke patients can be challenging, especially in aphasic patients. It is often difficult to separate abulia, labile pseudobulbar affect, and aprosodia resulting from the stroke itself from depressive symptoms. Depression should be suspected in stroke patients who are not making expected recovery, lose previously acquired milestones, or those with reduced initiation and minimal participation in rehabilitation. Selective serotonin reuptake inhibitors (SSRIs) are effective and safe in treating post-stroke depression. Psychological support, encouragement, and promoting the patient's independence are important. Psychostimulants, such as methylphenidate, may be considered in some patients.

24.2.7.2. Fatigue

Patients commonly report subjective fatigue, exhaustion, and lack of energy after stroke. The etiology of post-stroke fatigue is poorly understood, but is likely to be multi-factorial. Patients with pre-stroke fatigue, depression, and severe disability are at risk (Choi-Kwon et al., 2005). Stroke-related cognitive sequela and sleep disorders may also contribute. Staub and Bogousslavsky (Staub and Bogousslavsky, 2001) introduced the concept of "primary" post-stroke fatigue, and postulated that it may be linked to attentional deficits resulting from interruption of neural networks involved in tonic attention, such as the reticular activating system and related structures involved in the subcortical attentional network. Post-stroke fatigue may limit the patient's ability to return to previous activities. The recognition of post-stroke fatigue may be critical during recovery and rehabilitation after stroke. Treatment is cause-specific. The use of anti-fatigue pharmacotherapy, in a matter akin to treatment of fatigue in other neurological disorders, may be considered.

24.2.8. Gastrointestinal complications

24.2.8.1. Gastrointestinal hemorrhage

Gastrointestinal hemorrhage is a serious complication that occurs in 3–5% of acute stroke patients. It is often attributed to the stress of the stroke event "stress/Cushing's ulcer," but other factors such as use of antithrombotics or steroids may contribute. Older patients, and those with increasing stroke severity or altered level of consciousness, are particularly at risk. Prophylactic use of H2 antagonists is recommended for all stroke patients, especially those who are not receiving enteral feeds and those with reduced level of consciousness. Withholding of antithrombotics in stroke patients who develop GI bleeding should be determined on a case-by-case basis.

24.2.8.2. Constipation

Constipation is common among stroke patients. In a study of 140 patients with ischemic stroke, constipation was the most common complication during inpatient rehabilitation affecting 23% of patients (Doshi et al., 2003). Immobility after stroke, dehydration, malnutrition, and nasogastric formulations can all contribute to constipation. Constipation may be associated with significant morbidity, such as confusion, abdominal obstruction, vomiting, and decreased appetite, which can adversely affect the recovery process. Early mobilization, adequate hydration, use of appropriate nasogastric formulations, and use of laxatives or enemas when necessary are important preventive and therapeutic approaches.

24.2.9. Endocrine and metabolic complications

24.2.9.1. Hyperglycemia

Hyperglycemia is present in up to 40% of patients with acute ischemic stroke and subarachnoid hemorrhage, regardless of diabetic status. It may reflect elevated sympathoadrenal tone, increased stress hormones such as cortisol and noradrenaline, or damage to central autonomic control sites. In a study of 41 patients with ischemic stroke, the median admission glucose was significantly higher in patients with insular cortical ischemia compared with those without acute ischemia, suggesting that involvement of the insular cortex may contribute to post-stroke hyperglycemia (Allport et al., 2004). Although it has been demonstrated that persistent post-stroke hyperglycemia is associated with a worse prognosis, the beneficial value of controlling blood glucose following stroke on outcome is yet to be proven.

24.2.9.2. Malnutrition

Malnutrition is an important yet frequently overlooked complication of stroke. Elderly patients who were malnourished before their stroke, and those with depressed consciousness, dysphagia, perceptual or motor deficits, depression, or bowel impaction are particularly at risk. Poor nutritional status can have adverse effects on immune, cardiac and gastrointestinal systems, bone

metabolism, and tissue repair. In one study, low serum albumin, which is an index of nutritional status, correlated with the frequency of medical complications in stroke patients (Dziedzic et al., 2004). It is, therefore, important to maintain an adequate nutritional status in patients with stroke. Supplemental vitamins may be required if food intake is poor. Early initiation of temporary nasogastric tube or percutaneous endoscopic gastrostomy feeding in patients who cannot swallow is recommended.

Protein-energy malnutrition can provoke non-thyroidal illness syndrome (NTIS), which is characterized by reduction of serum triiodothyronine (T3) without elevation of thyroid-stimulating hormone (TSH), in stroke patients. In one study, NTIS was detected in 83% of stroke patients, and free T3 levels were significantly higher in patients with improved functional outcome (Hama et al., 2005). Therefore, it may be important to determine whether NTIS is present and to ensure proper intensive rehabilitation and nutritional management.

24.2.9.3. Electrolyte disturbances

Fluid and electrolyte abnormalities, in particular hyponatremia, are common following stroke. Fluid often accumulates in the sacral region during prolonged bed rest. The development of hyponatremia is thought to be related to changes in the levels of atrial natriuretic factor and/or inappropriate secretion of antidiuretic hormone (ADH) after stroke, as a result of stroke-related elevations in serum catecholamines and cortisol, increased release of ADH, and resetting of osmoreceptors. Hyponatremia may be associated with significant morbidity, such as confusion, weakness, vomiting, and seizures, which can adversely affect the recovery process. It is important to ensure euvolemia, and to monitor electrolytes in stroke patients.

24.2.10. Musculoskeletal complications

24.2.10.1. Arthritis

Stroke patients may develop arthritis de novo or experience exacerbation of pre-existing arthritis in paretic limbs following their stroke. In a prospective study of 111 patients presenting with their first stroke and no history of previous arthritis, acute inflammatory and crystal arthritis were observed within a median of 8 days on the paretic side in 19 patients and on the non-paretic side in 4 patients (Chakravarty et al., 1993). Patients taking thiazide diuretics prior to their stroke are at increased risk for gout. The development of arthritis can prolong the length of inpatient hospital stay, and delay initiation of active rehabilitation and recovery. Treatment is symptomatic, and may include the use of NSAIDs, allopurinol, colchicines, or intra-articular steroids.

24.2.10.2. Hip fractures

Patients with stroke have a propensity to hip fractures. Most fractures occur on the hemiplegic side and are secondary to accidental falls. Hip fractures are four times more common in stroke patients compared to the general population, and represent 45% of all post-stroke fractures. This is attributed to loss of bone density after stroke and propensity to falls. The loss of bone density after stroke is multi-factorial, as a result of unloading of the skeleton at the affected side due to loss of mobility and function, and increased bone resorption in the first few months after stroke. Stroke as a condition is associated with an increased risk of falls from concurrent motor, sensory, and visuoperceptual deficits. Fallers are more likely to be depressed. Hip fractures in stroke patients result in greater mortality and morbidity than in those without stroke. Fall precautions are recommended for all stroke patients, especially those with neglect, anosognosia, or cognitive impairment. Measures to prevent bone loss and preserve bone architecture should be integrated into stroke care.

24.2.10.3. Limb or shoulder pain

The incidence of limb and shoulder pain on the hemiparetic side after stroke varies from 4% to 27% (Doshi et al., 2003). The primary cause is upper motor neuron paralysis of muscle groups supporting the shoulder, which leads to loss of mechanical integrity around the shoulder joint, shoulder sublaxation, and increases the risk of traumatic injury, inflammation, and soft tissue contracture. There are multiple causes of limb pain after stroke. These include brachial plexus and nerve stretch injury, frozen shoulder, shoulder spasticity, bursitis or tendonitis, shoulder–hand syndrome, and central thalamic pain syndrome. Shoulder pain during the initial flaccid stage of hemiplegia is often the result of a traction injury of soft tissue or nerve. Use of resting hand splints, shoulder supports, wheelchair arm support, and a daily passive range of motion exercises are important. Isolated shoulder pain often responds to analgesics, NSAIDs, local heat or ice application, and ultrasound therapy.

The shoulder–hand syndrome affects the shoulder, wrist and hand, and is characterized by pain, edema, and vasomotor changes in the affected limb. It occurs between 2 weeks to 3 months after onset of hemiplegia. The pain and tenderness are most pronounced when abducting, flexing, and externally rotating the arm.

The swelling is most evident over the carpal bones and distal hand joints. Early full range of motion exercises of the shoulder joint is important to prevent this complication. Early recognition is key, since it can result in muscle atrophy, osteoporosis, and contractures if untreated. Steroids, orally or via intra articular injections, and physical therapy are the mainstay of treatment. Anti-spasticity measures may be required. Stellate ganglion blockade is reserved for severe cases.

24.2.10.4. Nerve injury

Decreased movement and sensation can predispose to compression of peripheral nerves in patients with stroke. The superficial peroneal and ulnar nerves are most commonly involved. The development of femoral neuropathy should alert the physician to the possibility of retroperitoneal hemorrhage, especially in patients on anticoagulation.

24.2.10.5. Decubitus ulcers

Skin breaks and pressure sores occur in approximately 20% of stroke patients. They are preventable. Early mobilization, turning the patient every 2 hours, use of padded heel boots, and the use of special air-floatation mattresses can prevent the development of decubitus ulcers. Incontinence increases the risk for skin breaks. The skin should be kept clean and dry. Malnutrition plays a role in the formation of pressure ulcers and it is important to maintain adequate nutrition. The skin should be examined regularly, especially the sacrum, buttocks, and heels. When skin breaks do develop, treatment includes reducing pressure and friction, removing the necrotic debris, optimizing nutritional status, and managing bacterial contamination if present.

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Chapter 25

Anterior circulation syndromes

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The anterior circulation describes the cerebral areas supplied by the branches of the internal carotid arteries (ICA). The ICAs supply the majority of both cerebral hemispheres, except the occipital and medial temporal lobes, which are supplied by the posterior cerebral artery (PCA), usually a branch of the basilar artery (BA).

Ischemic strokes occurring in the anterior circulation are the most common form of all ischemic strokes, accounting for about 70% of all cases, referring to approximately 410, 000 new anterior circulation ischemic stroke cases per year in the USA (Broderick et al., 1998). Ischemic strokes in the anterior cerebral circulation may be from the occlusion of one of the major cerebral arteries or their superficial or perforating (penetrator) branches. In Caucasians, the most common cause of intracranial arterial occlusion is embolism (Caplan et al., 1986a). The source of embolism can be cardiac, such as atrial fibrillation related intracardiac thrombi (cardio-embolism); transcardiac, such as patent foramen ovale associated with deep vein thrombosis (paradoxical embolism); or proximal or parent artery lesions, such as aortic arc or cervical ICA steno-occlusive lesions (artery-to-artery embolism). Embolic occlusion commonly occurs at the intracranial arterial bifurcations and stem or divisions of the middle cerebral artery (MCA) (Caplan, 1993). The other major cause of anterior circulation ischemic stroke is large-artery steno-occlusive diseases. Compared to Caucasians, in whom the most common sites of atherosclerotic steno-occlusive lesions are the proximal 2 cm portion (bulb) of the ICA and the carotid siphon, Asians and Africans have higher rates of intracranial arterial steno-occlusive disease, located mainly in the stems of the MCA and anterior cerebral artery (ACA), and in the proximal portion of the BA (Caplan et al., 1986a). In addition to the emboli in distal cerebral circulations, larger-artery lesions may lead to ischemic stroke via thrombotic occlusion and hemodynamic or perfusion insufficiency. Atherosclerotic involvement of small branches or lipohyalinotic intrinsic disease of the penetrating vessels arising from the MCA, ACA, intracranial ICA and anterior choroidal artery (AChA) produce a lacunar type of stroke, which accounts for about one-fifth of ischemic strokes, and is different from embolic and large-artery-associated ischemic strokes in terms of prognostic and therapeutic aspects. The territory of the MCA is the most common site of anterior circulation infarction, accounting for approximately 90% of infarcts and two-thirds of all first strokes. Of MCA territory infarcts, 33% involve the deep MCA territory, 10% involve superficial and deep MCA territories, and over 50% involve the superficial MCA territory (Bogousslavsky et al., 1988). Occlusion of the ACA and AChA is infrequent (in approximately 2% and 1% of cases, respectively). Ischemia in the distribution of the ophthalmic artery is usually transient and results from ICA steno-occlusive lesions.

In this chapter, the clinical presentation patterns of the occlusion of arteries in the anterior circulation are reviewed in detail. It is important to note that acute ischemic stroke is a dynamic process, and varies markedly from patient to patient. Patients with similar clinical syndromes may have significantly different pathophysiological profiles. Therefore, every patient should be evaluated individually in terms of clinicotopographic and pathophysiological aspects. No strict templates of approaches are applicable.

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25.1. Internal carotid artery

25.1.1. Anatomy

The left common carotid artery (CCA) usually arises from the left side of the arcus aorta, while the right CCA arises from the innominate, or brachiocephalic, artery. At the carotid bifurcation, which is located in the level of thyroid cartilage, the CCA divides into the ICA and the external carotid artery (ECA) (Fig. 25.1). ICA anatomy is usually described by segmentation according to significant anatomical landmarks throughout its course. However, no uniform approach is available (Rhoton, 2002). We prefer to describe ICA anatomy by dividing it into seven segments: cervical (C1), petrous (C2), lacerum (C3), cavernous (C4), clinoid (C5), ophthalmic (C6) and communicating (C7) (Osborn, 1999) (Fig. 25.2).

After originating from the CCA, the first portion of the cervical ICA, known as the "carotid bulb," is significantly wider (7.5 mm, average diameter) than the CCA (7 mm) and distal ICA (4.7 mm) after the bulb.

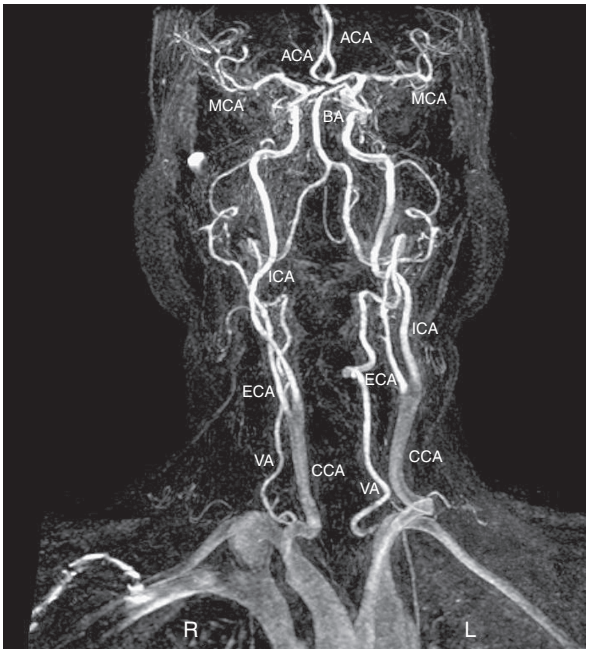

Fig. 25.1. A contrast-enhanced MR angiogram demonstration of the origins of the major craniocerebral arteries from arcus aorta; the cervical course of the carotid and vertebral arteries; the intracranial course of the internal carotid arteries, the basilar artery, and their main branches; and the connectiom creating the circle of Willis. MCA = middle cerebral artery; ACA = anterior cerebral artery; ICA = internal carotid artery; ECA = external carotid artery; BA = basilar artery; and VA = vertebral artery.

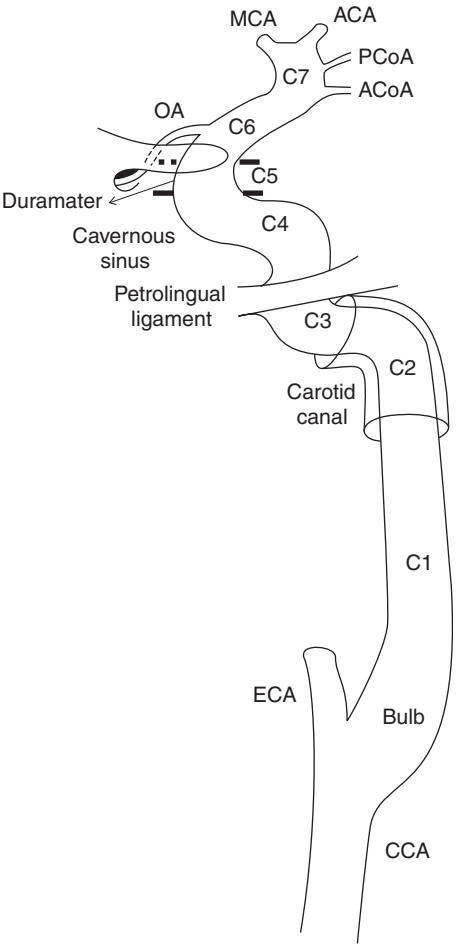

Fig. 25.2. Schematic representation (lateral view) of the seven segments of the ICA. MCA = middle cerebral artery; ACA = anterior cerebral artery; PComA = posterior communicating artery; AComA = anterior communicating artery; ICA = internal carotid artery; ECA = external carotid artery; CCA = common carotid artery; OA = ophthalmic artery.

The ascending part of the C1 segments of the ICA terminates at its entry to the carotid canal in the petrous bone. The petrous ICA (C2 segment) is the part of the artery that courses within the carotid canal. Two distinct subsegments (vertical and horizontal) and a junction between them (the ICA genu) are described. Two branches, the vidian artery (or artery of the pterygoid canal) and caroticotympanic arteries, arise from this segment. The next segment of the ICA, the lacerum (C3), extends from the caudal end of the carotid canal to the petrolingual ligament, without giving off any branches. The fourth segment (C4 or cavernous) of the ICA courses within the cavernous sinus. Branches arising from this segment are the meningohypophyseal artery, inferolateral trunk,

and capsular arteries. This ICA segment has three subsegments: the posterior ascending (vertical), horizontal, and anterior vertical portions. After this segment, the ICA passes through the dura mater forming the roof of the cavernous sinus. Following a short interdural segment (clinoid, C5), the ICA segment extending up to the posterior communicating artery (PComA) origin is called the ophthalmic (or C6) segment. The ophthalmic artery leaves the ICA at this segment. One or more superior hypophyseal arteries also arise from the C6 segment. After giving rise to the PComA and AChA branches, the last segment (C7) of the ICA is divided into its terminal branches at the intracranial bifurcation. The main continuing branch is the MCA, while the smaller ACA and the PComA form the anterior and posterior portions of the circle of Willis (Fig. 25.3).

When viewed laterally, the C4, C5, C6, and C7 segments have several curves that form an S-shape, and together these portions are called the carotid siphon. The lower half of the S, which is convex anteriorly, is formed by the cavernous segment. The upper half, which is convex posteriorly, is formed by the supraclinoid portions (Fig. 25.2). (Rhoton, 2002).

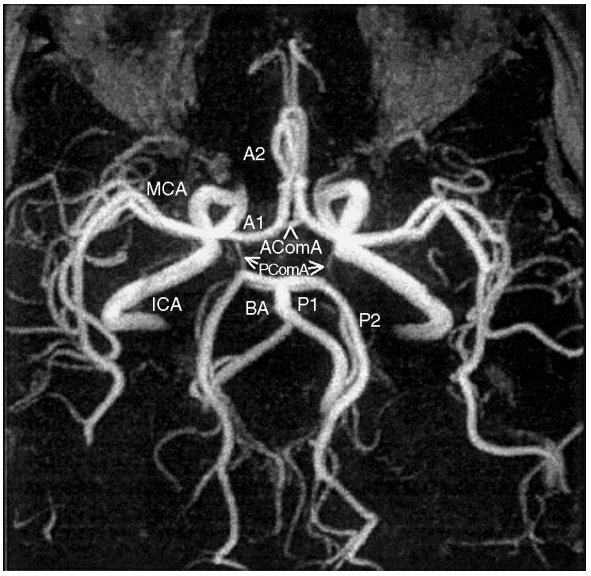

Fig. 25.3. Magnetic resonance angiographic depiction of the circle of Willis. Note that both PComAs are hypoplastic. MCA = middle cerebral artery; A1 = first or precommunicating segment of the anterior cerebral artery; A2 = second or post-communicating segment of the anterior cerebral artery; PComA = posterior communicating artery; AComA = anterior communicating artery; ICA = internal carotid artery; P1 = first or precommunicating segment of the posterior cerebral artery; P2 = second or post-communicating segment of the posterior cerebral artery.

Connecting the ACA with the AComA makes the anterior half of the Willis circle. In cases with hemodynamically significant cervical ICA stenosis, the most important source of collateral circulation for that hemisphere comes from the contralateral ICA via this pathway. In this case, the blood from the opposite ICA passes through the first segment of the ACA and then the AComA. Blood from AComA passes along the cortical branches of the contralateral ACA anterogradely, and along the first segment of the contralateral ACA retrogradely to the contralateral MCA, then distally into the territory of MCA in anterograde fashion. Connection of the vertebrobasilar system to the carotid system via the PComA forms the posterior part of the circle of Willis. The PComA is a branch of the terminal ICA and is connected to the PCA, one of the terminal branches of the basilar artery. In patients with significant ICA stenosis, flow from the BA via the PCA enters into the PComA, which supplies the MCA and ACA (Figs. 25.1 and 25.3).

The other collateral pathway is extracranial-to-intracranial through orbit. The facial branches of ECA linked to the ophthalmic artery branches. Blood flows in a retrograde fashion in the ophthalmic artery to reach the intracranial portion of the ICA at the siphon. From there, flow continues distally toward the circle of Willis in the usual anterograde fashion. The last collateral pathway is between pial branches of the PCA, MCA, and ACA over the convexity.

25.1.2. Clinical presentation of the internal carotid artery stenosis or occlusion

Atherosclerotic stenosis of the cervical ICA is a well-recognized cause of cerebral ischemia. Both embolic and hemodynamic, or low-flow, mechanisms are assumed to be the cause of stroke and transient ischemic attacks (TIAs) in ICA disease. The infarct pattern and related clinical syndromes are heterogenous in patients with acute ischemic from ICA stenosis. The competency of collaterals (the circle of Willis and the pial collaterals) and the degree of ICA stenosis can significantly affect the pattern of clinical presentation. The lesion size, localization, and distribution are also variable. With these variations in mind, relatively specific acute infarct patterns were described in stroke patients with significant ICA stenosis, particularly after the evolution of diffusion-weighted MRI in clinical practice (Szabo et al., 2001; Tsiskaridze et al., 2001; Kang et al., 2002). Patients with stenoocclusive lesions of the ICA can also present with TIAs, of which there are two types: hemispheric TIAs and transient monocular blindness or amarosis fugax.

25.1.3. Stroke patterns

There are five common acute ischemic stroke patterns in the patients with ICA stenosis (Ringelstein et al., 1983; Bogousslavsky and Regli, 1986; Bogousslavsky and Regli, 1992; Mournier-Vehier et al., 1995; Caplan, 2000; Szabo et al., 2001; Tsiskaridze et al., 2001; Kang et al., 2002; Chaves et al., 2003) (Fig. 25.4). A significant proportion of the patients have combined forms as well.

The first pattern is territorial infarction with cortical and/or subcortical involvement. The main mechanism is artery-to-artery or distal embolism. The common types of this pattern, all described in detail in this chapter, include occlusion of the carotid-T; ACA stem and cortical branches; and MCA stem, divisions, and cortical branches. More than one artery/branch occlusion can happen, and this is relatively indicative of proximal arterial steno-occlusive disease (Bogousslavsky, 1991b; Donnan et al., 1993a; Melo et al., 1992a).

The second pattern is subcortical infarction: the perforating deep arteries originated from ICA, ACA, and MCA stems are occluded. Hennerici and co-workers reformulated the mechanism underlying this subgroup as complete or partial MCA stem occlusion associated with well-functioning collaterals. Occlusion is either due to the embolization into the MCA, which results in a larger striatocapsular infarction, or due to the occlusion of one or a group of deep perforating arteries, leading to a smaller subcortical lesion (Szabo et al., 2001).

The third pattern is described as a combination of a relatively larger infarct (the first pattern) and smaller cortical and/or subcortical ischemic lesion(s). A partial embolism fragmentation or emboli shower of various sizes is suggested as the mechanism of this pattern (Szabo et al., 2001).

The fourth pattern is defined as multiple small strokes in the distal territories of the MCA and ACA. When seen in more than one arterial territory, particularly bihemispheric, this pattern is suggestive of cardio-embolism (Baird et al., 2000; Singhal et al., 2002; Kang et al., 2003). But, when seen in a single arterial territory, a parent artery steno-occlusive lesion is highly likely (Kastrup et al., 2002; Kang et al., 2003). Randomly distributed cortical small infarctions are seen. A possible cause is fragmentation of an embolus or multiple microemboli (shower) into the small vessels.

The last pattern is watershed infarctions. As mentioned in detail in the subsequent sections, there are two types of this pattern: the cortical watershed or external border-zone (located between the cortical territories of the ACA, MCA, and PCA) and the internal watershed or internal borderzone (located between the deep and superficial networks of the MCA and ACA). These lesions were traditionally believed to be caused by a hemodynamic or low-flow mechanism. However,

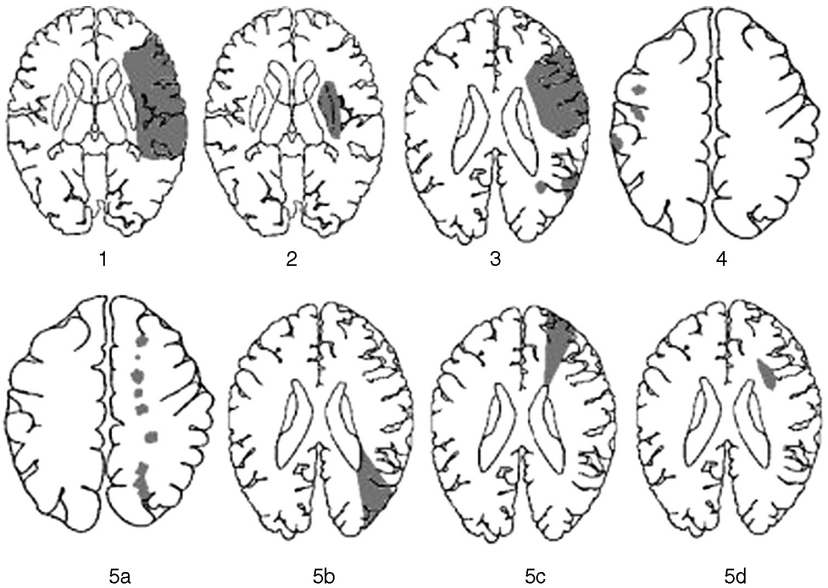

Fig. 25.4. Schematic illustration of the main stroke patterns associated with ICA stenosis/occlusion. Pattern 1: territorial infarction; pattern 2: subcortical infarction; pattern 3: combination of territorial infarcts and small cortical/subcortical infarcts; pattern 4: multiple small cortical/subcortical infarcts restricted to ICA territory; pattern 5: a = internal watershed infarct with rosary-like pattern; b and c = anterior and posterior cortical watershed infarcts; d = deep watershed infarct. Adapted primarily from Bories et al. (1985); Bogousslavsky and Regli (1992); Tatu et al. (1998); Szabo et al. (2001); and Kang et al. (2002).

an embolic mechanism has been increasingly mentioned as the main or a contributing cause of these infarctions (Caplan and Hennerici, 1998; Momjian-Mayor and Baron, 2005). A hemodynamic mechanism may be more important than embolism in internal borderzone infarcts while embolism may prevail in external borderzone infarcts (Momjian-Mayor and Baron, 2005).

25.1.4. Acute occlusion of the internal carotid artery

The clinical spectrum of occlusion of the cervical ICA varies from nothing (asymptomatic ICA occlusion) to a catastrophic panhemispheric infarction. In the most extreme cases there may be deterioration of consciousness, homonymus hemianopsia of the contralateral side, contralateral hemiplegia and hemisensory disturbance, and gaze palsy to the opposite side. Occlusion in the dominant hemisphere results in global aphasia, while occlusion in the nondominant hemisphere causes hemineglect. The clinical features are almost similar to those of the MCA proximal occlusion.

In the occlusion of the intracranial ICA bifurcation, also called carotid T-occlusion, the blood flow to both the MCA and ACA is interrupted, resulting in a combined ACA plus MCA territory infarct if the ACA is not sufficiently perfused by contralateral ACA via AComA. In the patients with ipsilateral fetal-type PCA, the infarct will then be panhemispheric, involving both ACA and PCA territories in addition to large MCA stroke (Fig. 25.5). The clinical spectrum of these two

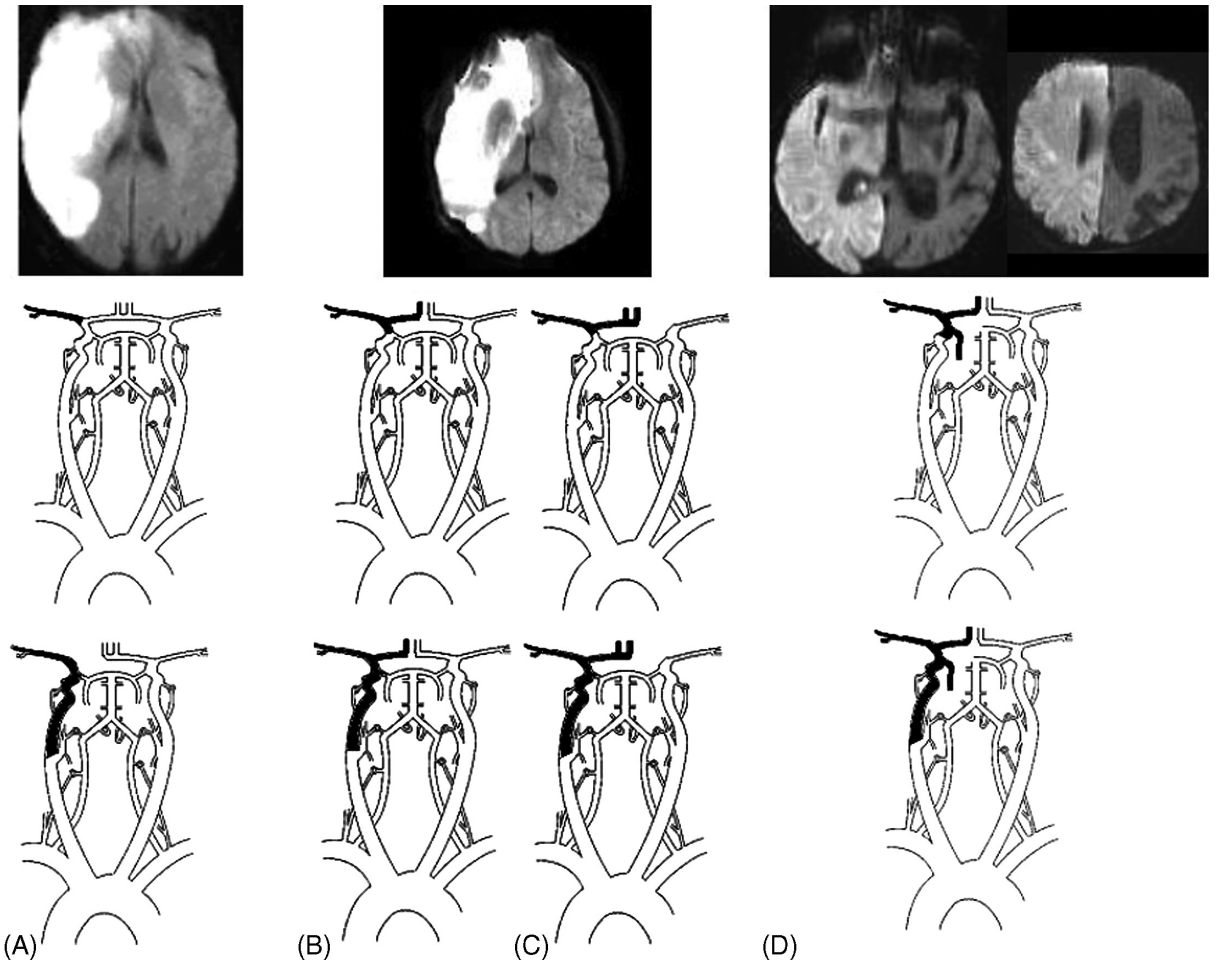

Fig. 25.5. Diffusion MRI and possible arterial occlusion patterns in three patients with acute carotid occlusion. (A) MCA stem or carotid-L occlusion; malign MCA infarction with sparing of the ipsilateral ACA territory indicating a functional AComA feeding the distal territory of that ACA. (B) Carotid-T occlusion; a combined MCA and ACA complete infarct indicating nonfunctional anterior Willisian collateral pathway. Extention into the contralateral ACA (also may be from singulate herniation) and the ipsilateral posterior cortical watershed is noted. (C and D) A panhemispheric infarction indicating a fetal PCA, which is occluded in association with the MCA and ACA, and absence of an operating AComA and PComA.

types of large infarctions is similar to that of the malignant MCA syndrome (see later in this chapter).

One of the distinguishing features of ICA occlusion from the MCA stem syndrome is the presence of ocular symptoms. Albeit rare, the simultaneous occurrence of transient monocular blindness (amarosis fugax, see later in this chapter), retinal embolic infarctions, or ischemic optic neuropathy together with contralateral hemiplegia and other hemispheric symptoms indicates thrombotic ICA occlusion (Bogousslavsky et al., 1987b). It is important to note that the distal extent of the thrombus occluding the ICA may end at the level of the ophthalmic artery when it serves as an extracranial-to-intracranial collateral pathway. In the absence of functioning collaterals via the ophthalmic artery and PComA, the occluding ICA thrombus is expected to reach up to the level of the carotid-T. The intracranial extension of this thrombus is determined mainly by the reversed flow in the ipsilateral ACA via the AComA. The vast majority of the carotid T- or L-occlusions are embolic in origin, therefore the ophthalmic artery is usually patent.

Additionally, a partial Horner's syndrome may develop on the side of the cervical ICA occlusion because of the involvement of sympathetic fibers on the internal carotid artery wall. There may be engorgement of conjunctival and episcleral vessels, corneal edema, and rubeosis iridis. Some patients may complain of orbital pain, which is often relieved by transition to the supine position. Asymmetric hypertensive changes may be noted on fundoscopy. Corneal arcus senilis may also be less apparent on that side (Brazis et al., 1996; Caplan, 2000). And also, palpation of the neck is suggested to reveal absent carotid pulsations at the angle of the jaw (Fisher, 1961). It is important to note that this occurs only when the CCA is occluded. However, when the ICA is occluded, the patent and somewhat externalized CCA pulse is usually transmitted to the ICA region in the neck. Therefore, palpation of the pulse on the ICA region does not exclude cervical ICA occlusion. Sometimes, ophthalmic collaterals from the facial branches of the ECA may be palpable at the angular, brow, and cheek regions (Caplan, 2000).

Compared to the less severe cervical ICA stenosis, territorial (pattern 1) and watershed (pattern 5) infarctions are more frequent stroke patterns in acute cervical ICA occlusion (Szabo et al., 2001). However, embolic patterns can also be seen (Kang et al., 2002). The source of emboli might be fragmentation of thrombus at the time of, or shortly after, acute carotid occlusion. Embolization may also arise from the stump of the ICA, where the Venturi effect of the blood passing up to the CCA to the ECA may sweep material from the stump distally to reach the intracranial arteries (Barnett et al., 1978).

Acute ICA occlusion with large cerebral infarction typically has a poor outcome. The presence of global aphasia, loss of consciousness at onset, and headache at presentation are all associated with a worsening prognosis. Emboli- or dissection-related ICA occlusion can have a poorer prognosis in comparison with atherothrombotic occlusions (Milhaud et al., 2002). One of the reasons is shift or mobilization and expansion of the watershed area seen in patients with long-duration atherosclerotic ICA diseases.

25.1.5. Hemispheric carotid TIAs

Hemispheric carotid TIAs are typically brief, usually lasting 7–10 minutes, as described by patients retrospectively (Bousser et al., 1981). Overall, 90% of carotid spells last less than 6 hours. Contralateral motor and sensory dysfunction is the most frequent presenting mode. Pure motor dysfunction, pure sensory dysfunction, and pure aphasia can occur (Pessin et al., 1977). Isolated distal extremity weakness (arm, hand, and leg) has been reported, and may be the only manifestation (Futty et al., 1977). The severity of motor dysfunction varies from minimal weakness to dense hemiplegia. Dysarthria is reported by nearly one-fifth of patients with hemispheric carotid TIA. Approximately half of patients with dominant hemisphere carotid TIA experiences dysphasia (Futty et al., 1977). Patients with transient hemiparesis who were anosognosic for the hemiparesis were described (Grand Maison et al., 1989). It is difficult to diagnose retrospectively from an unwitnessed history, however, transient anosognosia that can be diagnosed when the patients are witnessed when symptoms occur (Price et al., 1977; Johnston et al., 2000).

An uncommon but relatively characteristic manifestation of carotid TIA is paroxysmal limb shaking (Baquis et al., 1985; Yanagihara et al., 1985; Bogousslavsky and Regli, 1986; Tatemichi et al., 1990; Firlik et al., 1996; Leira et al., 1997; Klempen et al., 2002; Schulz and Rothwell, 2002; Chaves et al., 2003). Typically, it is associated with contralateral severe carotid stenosis or occlusion, resulting in significant hemodynamic compromise. The underlying pathophysiology is not clearly defined, but may be similar to that proposed for convulsive syncope (Feldmann and Wilterdink, 1991); namely recurrent, brief, involuntary, coarse, irregular or rhythmic wavering movements of the arm and the leg. Patients describe these movements as shaking, trembling, twitching, or flapping. Their frequency is between 3 and 12 Hz (Yanagihara et al., 1985), and their duration varies from several seconds to several minutes. The face is usually spared, but

the limbs can be involved bilaterally (Baquis et al., 1985). There is no loss of consciousness during the episodes. Speech difficulty or weakness is not usually observed during the attacks. However, mild transient hemiparesis can be noted immediately after the episodes. The frequency of the episodes varies from once a week to ten times a day (Baquis et al., 1985; Yanagihara et al., 1985; Tatemichi et al., 1990).

Despite the apparent clinical resemblance to partial motor seizures, limb-shaking carotid TIAs are not epileptic in origin. Firstly, these spells are characteristically orthostatic, or precipitated by standing, walking, or neck hyperextension. Transition into the supine or sitting position usually relieves this symptom (Yanagihara et al., 1985; Tatemichi et al., 1990). It is noteworthy that there is usually no associated orthostatic hypotension or blood pressure drop in these patients. However, these symptoms can sometimes occur independently of positional changes (Baquis et al., 1985). Secondly, limb shaking TIAs show no Jacksonian march and do not extend to the face (Schulz and Rothwell, 2002). Thirdly, interictal and ictal EEGs were reported to be normal (Baquis et al., 1985; Yanagihara et al., 1985). Moreover, antiepileptic medications are not beneficial, but many patients become asymptomatic after carotid endarterectomy. Some patients may benefit from antihypertensive medicine withdrawal or raising blood pressure (Tatemichi et al., 1990, Leira et al., 1997).

Patients with hemispheric carotid TIAs have a higher risk of subsequent stroke and death compared with those presenting ocular carotid TIA or vertebrobasilar TIA. In addition to symptom duration and the presence of risk factors such as age and diabetes mellitus, two characteristic symptoms of hemispheric carotid TIA (hemiparesis and speech impairment) have been reported as predictive factors for subsequent stroke risk (Johnston et al., 2000; Rothwell et al., 2005).

25.1.6. Monocular blindness and ocular stroke

Transient or permanent monocular blindness (TMB or PMB) is usually associated with disease of the cerebral anterior circulation system, and ischemia of the retina or optic nerve. Ocular symptoms are a warning of an impending stroke of the brain or the eye. Monocular blindness of the eye and optic nerve can be differentiated regarding their clinical manifestations. Physical examination of the vascular system and the eye is crucial after ocular signs.

Transient monocular blindness or amaurosis fugax may occur frequently isolated or sometimes with cerebral symptoms. It may recur over a period of hours, days, and weeks. The characteristic of the attack and duration of the visual disturbance are summarized in Table 25.1. Amaurosis fugax can be classified into four types: type I is developed by transient retinal ischemia; type II by retinal vascular insufficiency; type III by vasospasm; and type IV occurs due to antiphospholipid antibodies and unknown causes (Table 25.1) (Burde, 1989; Wray, 2001).

25.1.6.1. Transient monocular blindness type I

The onset is sudden, with partial or complete dimming or obscuration of vision, lasting seconds to minutes. Partial impairment is defined as greyout, or an ascending or descending curtain or a movement sideways across the eye. Patient may describe moving tracks of light

Table 25.1

Types of transient monocular blindness*

	Type I	Type II	Type III	Type IV
Onset	Sudden	Less rapid	Sudden	Sudden
Visual field	All or partial	All or partial	All or progressive	As type I, II, or III
Visual loss	May black out Completely Provoked	Loss of contrast vision photopsia, sunlight	May spare fixation photopsia, scintillating sparkles	May alternate between eyes
Length	Seconds or minutes	Minutes or hour	Minutes	Any length
Recovery	Complete	Complete	Frequently complete	Complete
Pain	No	Rare	Often	Pain
Mechanism	Retinal ischemia Embolus, arteritis	Carotid occlusive disease	Vasospasm, migraine	APS, idiopathic

*Wray (1988), Burde (1989). APS = antiphospholipid syndrome.

without headache (Fisher, 1952; Wilson 1979). Contralateral hemiplegia may accompany the blindness (optico-cerebral syndrome). The cause of fleeting blindness is propagation of thrombus in the ICA over an atherosclerotic plaque, leading to periodic reduction in blood flow and reduced pressure in the ophthalmic artery, with transient ocular ischemia as a consequence. Embolization of the carotid artery, the central retinal artery (CRA) and the posterior ciliary artery may develop by the thrombus and cholesterol particles originating from the ulcerating plaques of the aorta or carotid arteries (Fisher, 1959; Beal, 1981). TMB has been considered as one variety of carotid artery TIA. In high-grade carotid stenosis or impending CRA occlusion crescendo TMB may occur, and examination of the large arteries of the head, neck, and eyes should be performed to localize the lesion in the ICA (Fig. 25.6).

ICA dissection is another cause of TMB, the patient presenting with ipsilateral neck, retro-orbital and head pain, miosis, partial ptosis in the ipsilateral eye, and anisocoria with normal pupil reflexes indicating an oculosympathetic palsy (Horner's syndrome). After a latent period the patient may have a TIA such as transient hemiparesis or TMB. Visual symptoms following ICA dissection are described as visual scintillations and bright sparkles, reminiscent of migraine (Ojemann et al., 1972; Caplan, 1993).

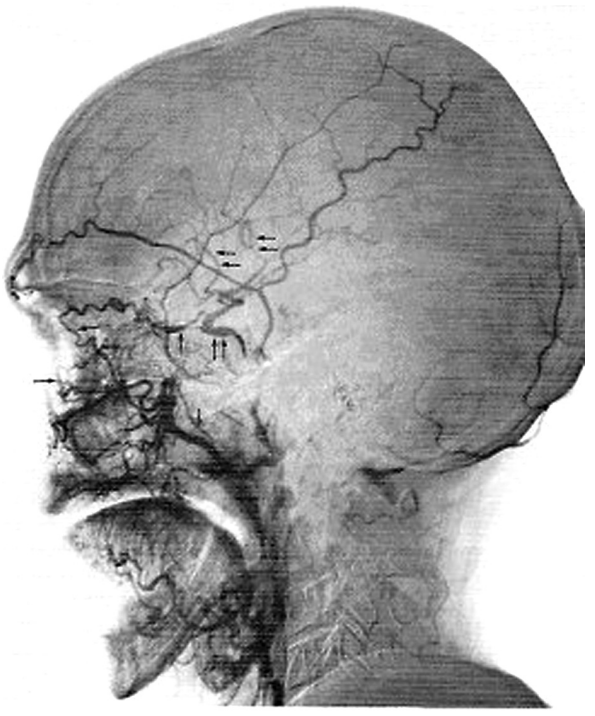

Fig. 25.6. The carotid artery is occluded and the ophthalmic artery is dilatated and its retrograde filling is delayed.

The inflammatory disease giant-cell arteritis may cause TMB by involvement of CRA or the posterior ciliary artery, and may lead to infarction of the optic nerve head (anterior ischemic optic neuropathy). In addition, it may affect branches of the ECA, especially superficial temporal and occipital arteries, causing headache, scalp tenderness, claudication of the jaw, and tenderness over the affected temporal artery. The characteristic laboratory findings are high erythrocyte sedimentation rate (ESR) with normochromic anemia, increased alkaline phosphatase level and fibrinogen level. Treatment should be started if the fibrinogen level is increased with or without increased ESR (Hayreh, 1971).

The antiphospholipid antibodies may also give rise to TMB. There are several studies, given increased rate of thrombosis in patients with these antibodies, that suggest a causal role for antiphospholipid antibodies in cerebral/ocular stroke or TIA/TMB. The antiphospholipid antibodies are a group of immunoglobulins, including the lupus anticoagulant and anticardiolipin antibody. Patients having these antibodies may have a history of certain clinical events, such as cardiac valvular abnormalities, thrombocytopenia, recurrent venous or arterial stroke, and spontaneous abortion. Patients with antiphospholipid antibody syndrome may display monocular total visual loss from the bottom-up, from the top-down, or episodic unilateral altitudinal or central visual deficits typically lasting a few minutes (Digre, 1989; Coull et al., 1992).

Hematological conditions affecting small arteries, such as sickle-cell disease, polycythemia, and nonarteriosclerotic vasculopathies including fibromuscular dysplasia, systemic lupus erythematosus, moya-moya disease, granulomatous angiitis, congophilic angiopathy, have been associated with TIAs and TMBs (Bruno et al., 1992; Burde, 1993; Greven et al., 1995) (Table 25.2).

To detect the cause of blindness, the following tests should be performed: auscultation of the heart, neck, and head; noninvasive investigations of the carotid artery by B-mode scans, Doppler color-flow imaging, and oculoplethysmography; angiographic examination of the head and neck by magnetic resonance angiography and/or CT angiogram; when indicated, stroke profile by diffusion or perfusion-weighted MRI studies; digital substraction arteriography in patients who are candidates for carotid endarterectomy or in those with ICA dissection if MRA and ultrasound are inadequate; cardiac evaluation by two-dimensional transthoracic and transesophageal echocardiogram and Holter monitoring; complete blood tests including prothrombin

Table 25.2

Causes of transient or permanent ocular blindness

Large-artery disease	
Local atherothrombosis of ICA	
Artery-to-artery embolism from ICA	
Propagation from ICA occlusion	
Cardioembolism	
Atrial fibrillation	
Rheumatic disease	
Myxoma	
Acute or subacute endocarditis	
Floppy mitral valve	
Mural thrombus	
Others	
Fibromuscular dysplasia of ICA	Moyamoya disease
Dissection	Antiphospholipid antibody(s)
Chronic i.v. drug users	Wegener's granulomatous angiitis
Lupus erythematosus	Disseminated intravascular coagulopathy
Behçet's syndrome	Long-bone fractures

time, partial thromboplastin time, platelet count, Westergren ESR, fibrinogen level, blood sugar, cholesterol, triglyceride and blood lipids, and when indicated, antiphospholipid antibodies, protein C, protein S and antithrombin III levels (Ackerman, 1979; The Amaurosis Fugax Study Group, 1990; Wrays, 2001).

25.1.6.2. Transient monocular blindness type II

In this type of TMB the visual loss is less rapid in onset (over 5 minutes) and longer in duration (minutes to hours). Visual acuity is altered but visual acuity is not affected. Sight becomes fragmented and patchy, and the patients describe the appearance as a photographic negative. Bright objects become brighter and dark objects may become more difficult to see. Patients describe a transient closing-in of the peripheral vision or a dull pain over the eye. Tight stenosis of the ipsilateral ICA and ECA due to retinal insufficiency is the likely cause. Systemic hypotension, venous hypertension, and extracerebral steal are conditions that provoke attacks of type II TMB (Russell and Page, 1983; Bruno, 1990).

The mechanism of visual loss is retinal in origin, and a low retinal arterial pressure is frequently present. Venous stasis retinopathy develops, presenting with unilateral microaneurysms, multiple small-blot-like intraretinal hemorrhages, segmental narrowing and dilatation of the veins, and ischemic disk swelling (Kearns and Hollenhorst, 1963). Fundus fluorescein angiography using intravenous fluorescein is indicated in those patients to determine the retinal microcirculation and the severity of impaired retinal hypoperfusion and vascular insufficiency.

25.1.6.3. Transient monocular blindness type III

This type of TMB may occur following vasoconstriction of the retinal vessels. Temporary vasospasm may be a plausible explanation for TMB in migraineurs. The pattern of visual loss is constricting or diffuse in type. Patients may have 1–12 brief episodes of TMB per day. Fundus photography taken at the end of the attacks reveals dilatation of arteries with segmental and persistent narrowing of arteries (Bruno et al., 1990; Burger et al., 1991). The diagnosis of TMB type III should be made when all other causes of visual loss are excluded and examination of the eyes are normal.

25.1.6.4. Transient monocular blindness type IV

Patients with type IV TMB have episodic visual loss resembling the visual type obscurations of type I, but the duration of the attack is too long (30–60 minutes) or too short (seconds). The visual abnormality resembles the transient loss of contrast vision typical of type II or photopsias and scintillations of vasospastic type III. The mechanism of this TMB is unknown, although some authors consider TMB in these patients as a possible variant of acephalgic migraine (Carroll, 1970; Corbett, 1983; Tomsak and Jergens, 1987).

25.1.6.5. Acute monocular blindness

Abrupt monocular blindness is the main symptom of ocular stroke, causing permanent visual loss. Infarction of the optic nerve can result from infarction of the (1) central retinal artery; (2) ophthalmic artery; and (3) branch retinal artery.

25.1.6.5.1. Central retinal artery occlusion

The onset is sudden and abrupt vision loss is infrequently accompanied by pain. Crescendo-type TMB may predict occlusion of the CRA. The main clinical sign of CRA occlusion is an amaurotic pupil, characterized by absent constriction to light on direct illumination, intact consensual light response, and intact near response when the eye is completely blind. After one hour or more, the ischemic retina takes on a white ground-glass appearance, and the normal red color of the choroid showing through at the fovea accentuates the central cherry-spot at the macula. Over the next few days, the cherry-red spot, the retinal opacification,

and the nerve fiber layer striations disappear, and optic atrophy of the optic disc of the primary type becomes prominent (Howard and Russell, 1987) (Fig. 25.7). The causes of occlusion are thrombo-embolic occlusion, in situ thrombosis, and inflammatory arteritis such as thromboangiitis obliterans, polyarteritis nodosa, giant-cell arteritis, arterial occlusion that occurs hydrostatically due to high intraocular pressure of glaucoma or low retinal blood flow of carotid stenosis, or aortic arch syndrome (Zimmerman, 1965; Brown et al., 1986; Coppeto et al., 1985). The source of embolus may be cardiac or intra-arterial from atheromatous ulceration of the aorta or ICA, ipsilateral ICA dissection, or from the stump of a thrombosed ICA.

25.1.6.5.2. Ophthalmic artery occlusion

Clinical signs of ophthalmic artery (OA) occlusion are similar to CRA occlusion, and produces opacification of the infarcted retina. Visual loss is typically severe and permanent, and most eyes have no light perception. Eye pain and pupillary dilation from concurrent ischemia to the ciliary ganglion or iris sphincter may develop in the acute phase. Fundoscopic examination reveals constricted retinal arteries and the optic disc may or may not be swollen. Within days, patients develop optic atrophy of the primary type, diffuse pigmentary degeneration, and arterial attenuation. In isolated cases of OA occlusion visual acuity recovers from light perception to 20/30 or from counting fingers at 6 inches to 20/50 with the restoration of retinal and choroidal blood flow (Duker and Brown, 1988). In fundus fluorescein angiography there is delayed filling in both choroidal and the CRA circulation. The cause of OA occlusion is mostly a thrombus originating in the artery itself, or a thrombus from distant site such as the common carotid artery, the aorta or the heart, or a thrombus propagated from an occluded ICA.

25.1.6.5.3. Branch retinal artery occlusion

The initial symptom is an abrupt and permanent loss of a sector of the visual field corresponding to the branch of the CRA involved. The main mechanism of retinal embolus is cholesterol emboli (Hollenhorst plaques) which are markers of atherosclerosis associated with bilateral carotid artery disease, and asymptomatic retinal cholesterol embolism is a independent predictor of stroke. Circulating microemboli are called "migrant pale emboli," are composed of platelets, and associated with thrombocytosis. Sources of cardio-embolism include mural thrombus, atrial fibrillation, heart surgery, cardiac myxoma, and myocardial infarction. Platelet-fibrin emboli appear as dull grey–white plugs that resemble a long white worm slowly passing through retinal arteries (Fig. 25.8). They tend to lodge at bifurcation, and then pass on gradually, fragmenting and resolving over time (Merchut et al., 1988; Chawluk et al., 1988).

25.1.7. Ischemic optic neuropathy

Ischemic optic neuropathy (ION) is the most common cause of abrupt permanent visual loss in patients past middle age (Ellenberger et al., 1973). Anterior

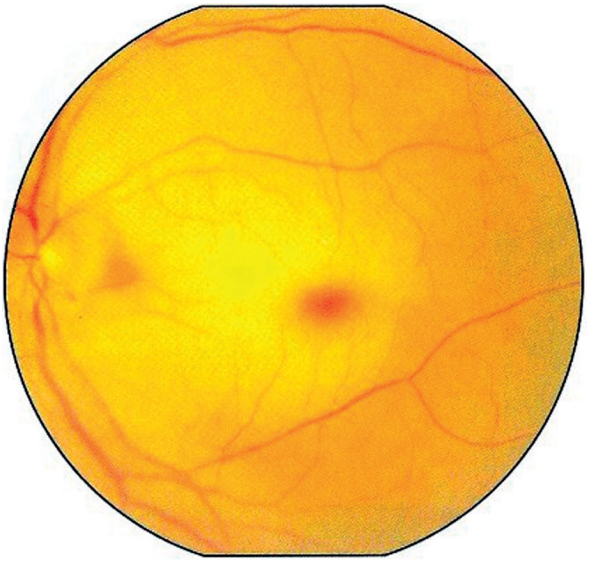

Fig. 25.7. Central retinal artery occlusion with a cherry-red spot and retinal edema.

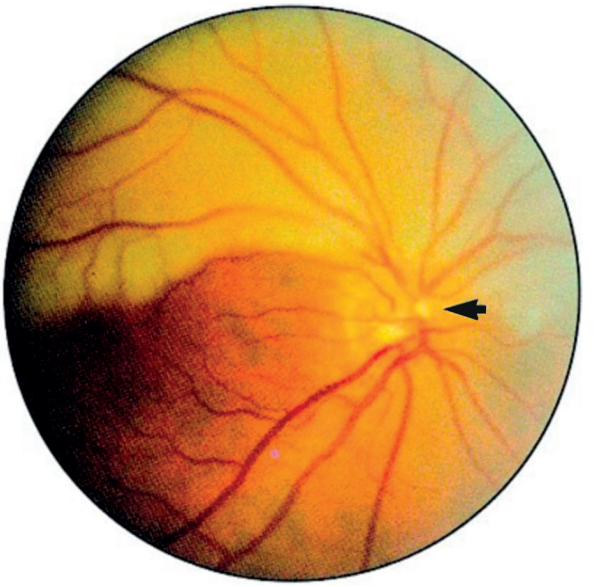

Fig. 25.8. Patient with branch retinal artery occlusion displaying hemispheric whitening of the retina from the occlusion. There is a plaque on the surface of the disk within the arteriole (arrowhead).

ischemic optic neuropathy (AION) corresponds to infarction of the anterior part of the optic nerve, and has visible optic pathology, swelling of the disk, and peripapillary hemorrhages. In acute AION, the optic disk is swollen either diffusely or focally. A diffuse swollen disk may mimic the appearance of papilledema. Single or multiple flame-shaped hemorrhages may be found in the peripapillary region and a few soft exudates. Posterior ischemic optic neuropathy (PION) is an infarction of the retrobulbar or intracranial optic nerve where there is no disk swelling or other fundoscopic signs acutely. The average age of onset is between 57 and 79 years with a peak range of 60–69 years. AION is more frequent than PION, accounting for 90% of cases of ION (Boghen and Glaser, 1975).

The main clinical features are (1) loss of vision, usually without pain; (2) visual acuity may drop suddenly or be progressive over 1–7 days; (3) altitudinal field defects observed in most patients (58–80%); (4) the affected eye presents with an afferent pupil defect (Boghen and Glaser, 1975; Repka et al., 1983). In patients with subsiding disk edema, optic disk pallor and atrophy may develop over a period of 4–6 weeks. AION with iris neovascularization (rubeosis iridis), in the absence of diabetic retinopathy, is a predictor of ipsilateral ICA occlusion (Carter, 1985) (Fig. 25.9). In acute PION following ischemia of the retrobulbar or intracranial optic nerve, the optic disk initially has a normal appearance. Therefore, AION is not distinguishable from PION by signs of ocular dysfunctions in the absence of acute ischemic optic disk swelling or retinal hemorrhages. Patients with ICA disease may have the simultaneous occurrence of cerebral borderzone infarct and ipsilateral either AION or PION, and is called opticocerebral syndrome (Bogousslavsky, 1987).

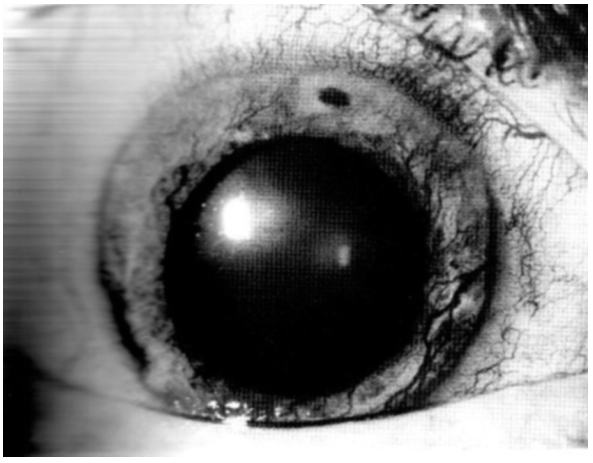

Fig. 25.9. Patient with rubeosis iridis due to neovascularization of the corpus vitrium and iris having internal carotid artery occlusive disease.

The most common causes of ION are: (1) nonarteritic occlusive disease with vascular risk factors such as ICA disease or small-artery disease with hypertension and diabetes (Young, 1981; Guyer et al., 1985; Sawle and Sarkies, 1987; Rizzo and Lessel, 1991; Chung et al., 1994); (2) giant-cell arteritis in older patients; (3) embolic occlusion of the posterior ciliary arteries as a complication of ipsilateral stenosis or occlusion and heart surgery (Zimmerman, 1965; Sweeney et al., 1982). The mechanism causing infarction of the optic nerve is the occlusion of two or more posterior ciliary arteries supplying the optic nerve. The critical region of damage is the prelamina, lamina, and immediate retrolaminal portion of the optic nerve (Onda et al., 1995). It has been suggested that the borderzone between the lamina cribrosa and centripedal branches of the pial vessels in the retrobulbar segment determines the site of infarction.

25.1.8. Borderzone (low-flow) infarcts

Unilateral or bilateral borderzone infarcts (BZ) occur between the distal branches of superficial or internal branches of two main artery territories. Subcortical BZ infarcts appear to lie in a deep vascular borderzone. They are localized in the distal ramifications of the lenticulostriate and medullar arteries of MCA (Adams et al., 1966; Fisher and McQuillen, 1981; Torvik, 1984; Angeloni et al., 1990; Graeber et al., 1992; Bladin and Chambers 1993; Gandolfo et al., 1998). Some authors called this type of infarct "low-flow infarction" or "hemodynamically induced infarction," to describe the underlying pathogenesis causing low-flow in the borderzone territories (Zülch, 1961). In thrombo-embolically induced infarcts, the corresponding cerebral arteries are occluded by emboli of various origin or by in situ atherothrombosis, while in borderzone infarction there is reduced cerebral blood flow and poor oxygen supply resulting from high-grade vascular lesions of the brain-supplying arteries in the neck, and rarely the common carotid or vertebrobasilar arteries. Subtotal stenosis or total stenosis, but not moderate stenoses, can generate a drop in perfusion pressure and ischemia severe enough that borderzone infarction develops.

Systematic prospective studies on BZ infarcts are sparse, but recent series found the frequency of this stroke type between 3% and 10% (Ringelstein et al., 1983; Kumral et al., 1998; Waterston et al., 1990; Bladin and Chambers, 1993). In a recent study, different types of BZ infarcts accounted for approximately 4% of all ischemic stroke visualized on MRI in an etiologically heterogenous stroke population (Kumral et al., 2004). The incidence of deep-subcortical borderzone

infarction is lower than anterior and posterior borderzone infarcts.

25.1.8.1. Causes of borderzone infarcts

The pathogenetically crucial parameter is the arterial perfusion pressure in BZ infarction. Arterial pressure will progressively drop downstream to an arterial stenosis beyond 80% reduction in its cross-sectional area. Following downstream blood flow decrease, arteries may collapse, as seen in arteriograms of ICA pseudo-occlusion (i.e. near-occlusion), and arterioles of the retina at the ipsilateral to subtotal ICA stenoses and occlusions may be filled during systole but collapse during diastole (Kleiser et al., 1991). A recent study showed that more than two-thirds of patients had occlusion or tight stenosis of the ICA and/or MCA ipsilateral to the BZ infarct, while only one-third of those with posterior BZ infarcts had vertebral or basilar artery stenosis or occlusion. One-fifth of patients with anterior BZ and one-third of those with subcortical BZ infarcts had proximal MCA stenosis, confirming previous data suggesting that MCA branch occlusions alone or with associated extracranial large vessel disease may result in these types of infarcts (Adams et al., 1966; Torvik, 1984; Angeloni et al., 1990). A low ventricular ejection fraction (LVEF) (<40%) was observed approximately in one-third of our patients with tight stenosis or occlusion of the ICA, and in 14% of those was associated with a source of cardio-embolism. Different potential mechanisms of BZ infarcts are listed in Table 25.3.

Table 25.3

Cause of borderzone infarcts

Carotid artery disease*
Tight carotid artery stenosis or occlusion
Artery-to-artery embolism from ICA#
Dissection
Moya-moya disease
Carotid clumping during endarterectomy
Carotid stenosis due to radiotherapy
Traumatic carotid lesion
Systemic arterial hypotension
Cardiac arrest
Cardiopulmonary bypass surgery
Abrupt drop of arterial pressure during antihypertensive therapy (in combination with severe carotid lesions)

*Atherosclerotic tight stenosis or occlusion of vertebrobasilar system may accompany.

#Embolic origin of border zone infarction may develop by showers of crystals or platelet-fibrin thrombi being transported into branches of the pial arteries to cause ischemic damage.

In patients with low-flow infarction, IA-DSA should be performed as soon as possible to detect pseudo-occlusion (i.e. near-occlusion). Magnetic resonance angiography (MRA) can be used as a noninvasive modality for visualizing the cerebrovascular anatomy and to determine the state of the collateral circulation (Razumovsky et al., 1999). Transcranial Doppler ultrasonography (TCD) is a noninvasive method transforming the static MRA picture into a dynamic evaluation of the cerebral circulation (Demchuck et al., 2000). TCD can demonstrate flow velocity, reversed high flow-velocity within a highly stenotic ICA, and collateral circulation (Ringelstein et al., 1983; Schneider et al., 1988; Powers, 1991; Ringelstein et al., 1994; Akopov and Whitman 2002; Vander Eecken & Adams 1953). The recruitment of collateral pathways in ICA occlusion or even in high-grade stenosis has great clinical importance (Rodda and Path, 1986; Harrison and Marshall, 1988; Weiller et al., 1991; Anzola et al., 1995). The sequence of recruitment of collateral pathways in ICA occlusions is, in descending order, the anterior communicating artery, posterior communicating artery, ophthalmic artery, and other minor external carotid artery branches such as the carotidotympanica arteries, rami tentorii, truncus meningohypophyses (Ringelstein, 1994). In the normal population, the circle of Willis is absent in 8–15% of cases, leading to an isolated middle cerebral artery or a combined isolated MCA plus ACA-trunk (Decker, 1963).

A recent study revealed that in patients with posterior BZ infarction, one-third had no ipsilateral PComA, and one-seventh had no AComA. In those with an anterior BZ infarct, half did not have an AComA that could be seen. Contralateral blood supply distal to the carotid artery stenosis by AComA was absent in half of patients with subcortical infarcts, and one-third of patients had neither a AComA nor a PComA. In three-quarters of patients with multiple BZ infarcts, the AComA or PComA were not visualized either unilaterally or bilaterally (Kumral et al., 2004). In a previous series, half of the patients had no collateral circulation distal to the occluded ICA, including the ophthalmic artery and AComA (Graeber, 1992). These data suggest that compensatory mechanisms by collateral circulation in the circle of Willis balancing downstream loss in perfusion pressure following a critical stenosis or occlusion are very crucial (Caplan and Hennerici, 1998; Razumovsky et al., 1999; Hendrikse et al., 2001). It is probable that the lack of AComA and PComA compensatory mechanisms is the main contributing factor in the development of BZ infarcts. In this unfavorable condition, the critical reduction of flow due to extracranial ICA stenosis or occlusion may lead more often to BZ infarction of the brain than with an intact interhemispheric cross-flow.

Cardio-embolism was considered a cause of BZ infarction that may occlude proximal or distal branches of the pial arteries, and result in hypoperfusion in a zone of marginal blood flow. In a series, only one-seventh of BZ patients had a source of cardio-embolism, and had either large-artery disease or a low cardiac output (Russell and Bharucha, 1978; Torvik and Skullerud, 1982; Rodda and Path 1986; Kelly et al., 2002; Kumral et al., 2004).

In patients with posterior BZ, LVEF decrease was more frequent (56%) than those with anterior or subcortical BZ infarcts, suggesting the level of cardiac output is more crucial for the perfusion pressure in the posterior BZ area. In summary, our TCD with MRA findings highlight variable infarct mechanisms in patients with different types of BZ infarct. This heterogeneity depends on the severity of intra- and extracranial occlusive disease, peculiarities of the collateral circulation in the circle of Willis, and inadequate recruitment of collateral pathways to the MCA territory with coexistence of low cardiac output. ICA dissection may cause BZ infarcts, due to the rapidity with which the occlusive process occurs, and the inability of the cerebral vasculature to recruit collateral pathways quickly enough (Weiller, 1991).

25.1.8.2. Symptoms and signs in borderzone infarcts

There are characteristic features in the history of patients, such as repetitive motor and sensorimotor TIAs due to hypostatic stress or positional cerebral ischemia (Bogousslavsky and Regli, 1986; Ringelstein and Stögbauer, 2001), slowly progressive visual loss in one eye due to chronic ophthalmopathy, monocular blindness following embolization of cardiac lesions to the retinal artery from the carotid artery, transient hemichorea in the deep borderzone infarction, transient upper limb tremor or limb shaking due to fluctuating cortical ischemia in the frontal parasagittal borderzone area or in the temporo-parieto-occipital triangle (Yanagihara et al., 1985; Waterston et al., 1990; Bogousslavsky and Regli, 1992). In subjects with preceding fluctuating, or repetitive cerebral or ophthalmic symptoms the clinically critical question is whether the patient suffers from a hemodynamically critical occlusion, or a still embolizing ICA pseudo-occlusion (Ringelstein et al., 1983). A patient with pseudo-occlusion would be a candidate for carotid endarterectomy whereas in the definite occlusion he/she would not be.

Borderzone infarcts can be divided into four different patterns according to the location of lesions and clinical signs (Romanul and Abramowicz, 1964; Mounier-Vehier et al., 1994; Ringelstein and Stögbauer, 2001): (1) an anterior BZ infarct is between the superficial territories of the middle and anterior cerebral arteries and displays a sagittal paramedian extension on CT or MRI; (2) a posterior BZ infarct is between the superficial territories of the middle and posterior cerebral arteries at the parieto-occipital junction; (3) a subcortical BZ infarct (so-called "terminal supply area infarction" or "subcortical low-flow infarction") lies between the superficial and deep territories of the middle cerebral artery, appearing as a chain-like hypodensity(ies) of more than 1.5 cm in diameter extending in a sagittal direction along the centrum semiovale on both CT scan or T2-weighted MRI. Unilateral and string-like small lesions strictly contradict a microangiopathic causality because diffuse small multiple lesions over both hemispheres suggest small-artery disease; (4) bilateral BZ infarcts were considered in patients with lesions in both hemispheres (Fig. 25.10).

In single unilateral anterior (precentral) or posterior (post-central) BZ infarcts sensorimotor symptoms appear as they would for any hemispheric stroke (Table 25.4). Forced eye deviation is transient and infrequent in hemodynamically caused strokes, contrary to infarctions of the territorial type (Ringelstein, 2001). Motor weakness is often incomplete, sparing the face (Fisher and McQuillen, 1981; Bogousslavsky and Regli, 1992). Mild strokes with only minimal neurologic deficits are common. Dissociated sensory deficits, a useless hand, and astereognosia may be seen with posterior BZ infarcts (Fig. 25.11).

Regarding neuropsychological deficits, in patients with left anterior BZ infarct, transcortical motor aphasia or atypical subtypes of Broca's aphasia may develop, presumably due to interruptions of pathways in the frontal lobe. In patients with left deep BZ infarcts, global aphasia, nonfluent aphasia with or without comprehension and/or repetition deficits, ideomotor apraxia, acalculia, and in those with right deep infarction anosognosia, neglect, dysprosody may occur depending on the extension of lesion (i.e., centrum semiovale, arcuate fasciculus).

Ischemic ophthalmopathy or ischemic oculopathy is a chronic progressive disease with a history of gradual, progressive loss of visual acuity in patient with critically reduced perfusion pressure due to ICA occlusion (Young and Uppen, 1981; Carter, 1985; Coppeto et al., 1985). Typical findings are neovascularization of the retina, corpus vitrium and iris (rubeosis iridis), secondary glaucoma, and cataract. Aggressive treatment by opening of the ICA stenosis will promptly improve visual acuity and can even restore vision to a recently blind eye (Ringelstein, 2001).

Patients with borderzone ischemia in the temporo-parieto-occipital triangle or frontolateral ischemia

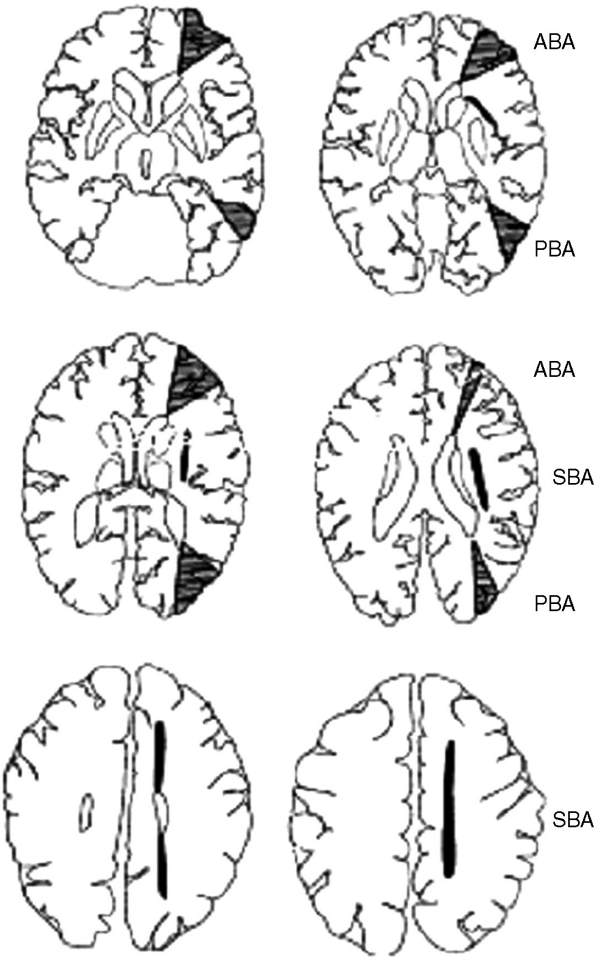

Fig. 25.10. ABA, Anterior (precentral) borderzone areas, PBA, posterior (post-central) borderzone areas and SBA, subcortical (low-flow territory) borderzone areas. Reproduced with permission from Bogousslavsky et al. (1986) and Bogousslavsky and Caplan (2001).

Table 25.4

Clinical syndromes following single or multiple borderzone infarcts

Single anterior cortico-subcortical infarcts
Somnolence, stupor
Brachial monoparesis
Crural sensorimotor hemiparesis
Brachiocrural hemiparesis
Transcortical motor aphasia
Focal myoclonic jerks
Single posterior cortico-subcortical infarcts
Sensorimotor hemiparesis
Hemihypesthesia
Wernicke aphasia
Transcortical sensory aphasia
Hemispatial neglect (tactile, visual, auditive), anosognosia
Hemianopia
Focal myoclonic jerks (limb shaking)
Bilateral lesions
Quadriplegia or triplegia
Paraparesis mimicking spinal stroke
Akinetic mutism
Apathia
Urinary of fecal incontinence
Focal myoclonic jerks

may have periodic or pseudoperiodic discharges which are often accompanied by contralateral or bilateral myoclonus of the paretic limb(s) or continuous contralateral focal motor seizures, simple partial seizures, or even secondary generalized tonic-clonic seizures, with eventual Todd's paresis or postictal deterioration of other focal deficits.

On release from hospital, more than half of the patients had no neurologic deficit or minor deficits. The relatively good prognosis of borderzone infarcts as compared to thrombo-embolic induced strokes has been emphasized (Ringelstein, 1983; Bogousslavsky and Regli, 1992). A favorable outcome is more likely

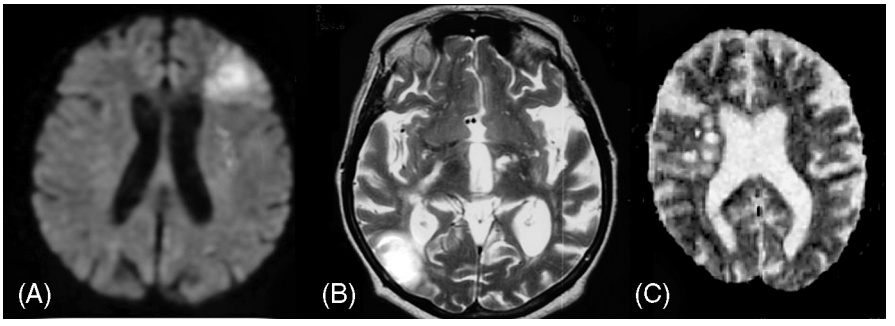

Fig. 25.11. (A) Diffusion-weighted MRI of the patient with anterior borderzone infarction between the boundary zone of the anterior and middle cerebral artery. (B) Posterior borderzone infarction at the middle cerebral artery and posterior cerebral artery on MRI. (C) Subcortical low-flow infarction on MRI. The lesion is chain-like arrangement along the lateral ventricle.

in patients with unilateral ICA occlusion but not in those with bilateral lesions (Hasegawa et al., 1992; Kleiser and Widder, 1992). Despite the relatively low rate of stroke recurrence, the general medical prognosis is not good. Deaths due to cardiovascular complications are frequent and account for an approximately 10% mortality per year (Bogousslavsky and Regli, 1986)

In patients with recent hemodynamic stroke, a high-grade stenosis should be operated. Progressive ischemic oculopathy is a strong predictor of neurologic and ophthalmologic stroke risk together with an extracranial ICA occlusion and insufficient circle of Willis, and requires prompt vascular surgical or interventional reconstruction of the intracranial or extracranial vessels.

25.2. Anterior cerebral artery territory syndromes

The ACA supplies all of the medial surfaces of the frontal and parietal lobes, the anterior four-fifths of the corpus callosum, the frontobasal cerebral cortex, the anterior diencephalon, and other deep structures. The lateral cortex alongside the interhemispheric fissure supplied by the ACA is wider anteriorly and narrows posteriorly. In subjects with the most extensive ACA distribution, the primary motor and sensory cortices are supplied by the ACA not only medially but also over the convexity as far as the inferior frontal sulcus. In patients with the least extensive ACA distribution, the ACA supplies little or none of the primary motor cortex, even medially. The ACA can be divided into a proximal or A1 segment, from its origin at the level of the anterior clinoid process to its junction with the AComA, and a distal artery segment after the AComA. The A1 segment passes over the optic chiasm or optic nerve varying in length from 7.2 to 18 mm (average 12.7 mm), and in diameter ranging from 0.9 to 4.0 mm (average 2.6 mm). In addition to Heubner's artery, the A1 and A2 segments give off smaller basal perforating branches, up to 13 from each A1 segment and up to 12 from each A2 segment (Perlmutter and Rhoton, 1976). The distal segment can be divided into: an A2 segment beginning at the AComA and passing in front of the lamina terminalis as far as the junction of the rostrum and genu of the corpus callosum; an A3 segment passing around the genu of the corpus callosum; an A4 segment from above the corpus callosum to beyond the central sulcus; and an A5 segment extending to the artery's termination (Foix and Hillemand, 1925; Critchley, 1930; Webster et al., 1960; Castaigne et al., 1972; Gacs et al., 1983).

25.2.1. Recurrent artery of Heubner

The recurrent artery of Heubner arises from the A1 segment of the ACA and supplies the head of the caudate nucleus, the anterior inferior part of the internal capsule's anterior limb, the anterior globus pallidus and putamen, and the anterior hypothalamus (Heubner, 1874). In different series, the frequency of absence varied between 0% and 35%. Its diameter ranges from 0.8–1.0 mm with a length of 20–23 mm. It penetrates the brain at the level of the lateral anterior perforating substance, medial Sylvian fissure, parts of the uncinate fasciculus, olfactory regions, or orbital frontal lobe, either as a single trunk or with as many as 12 branches.

25.2.2. Distal branches

The distal or cortical branches of ACA begin with the pericallosal artery at the AComA or at the point where ACA gives off the callosomarginal artery (the callosomarginal artery is absent in 18–60% of brains). In brains without a callosomarginal artery, all cortical branches originate from the pericallosal artery. The pericallosal artery runs above the corpus callous beyond the stria terminalis, passes around the splenium of the corpus callosum, and ends near the posterior choroids plexus of the third ventricle at the boundary of the posterior cerebral artery. Exceptionally, the distal pericallosal arteries run side by side, one is often posterior to the other and can shift across the midline, and occlusion of either artery can cause contralateral or bilateral infarction. The callosomarginal artery originates most often from the A3 segment of the ACA and coursing in or near the cingulate sulcus and giving off at least two major cortical branches. The anterior part of the callosomarginal artery is below the free margin of the falx, and the remainder courses above the free edge, with its displacement across the midline limited by the rigidity of the falx. Any or all branches of callosomarginal artery's branches supply the inferior frontal lobe (including the gyrus rectus, the orbital part of the superior frontal gyrus, the medial part of the orbital gyri, and the olfactory bulb), the medial surface of the hemisphere (including the cingulate gyrus, the superior frontal gyrus, the paracentral lobule, and the precuneus), the superior part of the lateral convexity (including the superior frontal, precentral, central and post-central gyri), and this part has anastomoses with branches of the middle cerebral artery. The band of lateral convexity supplied by the ACA is wider anteriorly than posteriorly and may extend into the middle frontal gyrus (Huber, 1982).

There are eight major cortical branches of the distal ACA originating either directly from the pericallosal artery or from its callosomarginal artery, although the number and site of these branches are variable: (1) the orbitofrontal (OF) artery arises from the A2 segment and supplies the olfactory bulb, the medial part of the orbital surface of the frontal lobe; (2) the frontopolar (FP) artery arises from the A2 segment and supplies the medial and lateral surfaces of the frontal pole; (3) the anterior internal frontal artery originates from the callosomarginal artery and supplies the anterior portion of the superior frontal gyrus; (4) the middle internal frontal (MIF) artery arises from the callosomarginal artery or A3 segment and supplies the middle portions of the medial and lateral surfaces of the superior frontal gyrus; (5) the posterior internal frontal (PIF) artery arises from the callosomarginal artery or A3 segment and supplies the posterior third of the superior frontal gyrus and part of the cingulate gyrus; (6) the paracentral (PC) artery originates from the A4 segment and supplies the paracentral lobule; (7) the superior parietal (SUP) artery originates from A5, A4, and supplies the superior portion of precuneus; (8) the inferior parietal (IP) artery arises from the A5 segment of the pericallosal artery (rarely from the callosomarginal artery just above the splenium of the corpus callosum) and supplies the posterior inferior part of the cuneus and adjacent portions of the cuneus (Krayenbuhl and Yasargil, 1968; Perlmutter and Rhoton, 1978; Gomes et al., 1984) (Fig. 25.12).

The ACA is the main artery supplying the rostrum, genu, body and splenium of the corpus callosum by short callosal arteries. Pericallosal artery branches pass through the callosum to supply the septum pellucidum, anterior pillars of the fornix, and the anterior commissure. The posterior part of the splenium is supplied by the pericallosal artery extending to the inferior surface of the splenium and all the way to the foramen of Monro. Some posterior parts of the splenum may take some small branches of the posterior cerebral artery (Table 25.5) (Perlmutter and Rhoton, 1978).

25.2.3. Variations and anomalies

The anatomy of the ACA is so varied among normal people that whether a variation should be called an anomaly is sometimes difficult to determine. The rates of variations reported in the literature have differed considerably. The A1 segment may be absent or nonfunctional threadlike, and both distal ACAs may fill from the larger A1 segment (Perlmutter and Rhoton, 1976; Crowell and Morawetz, 1977). The incidence of hypoplastic A1 varied between 2.0% and 11% and was often associated with additional anomalies of the ACA or the posterior cerebral, posterior communicating or basilar arteries in 82%. Among such anomalies, saccular aneurysms and ACA occlusion secondary to cardiac embolism accompanied by proximal hypoplasia of the contralateral ACA have been described. A1 segment duplication also occurs, as well as a third or median ACA arising from the AComA, which is sometimes as large as the two other ACAs and may supply the posterior medial hemisphere. Duplication of the AComA is present in 4.5–33.3% of the normal population, triplication in 6–10%, plexiform type in 6–9%, and it is absent in 0.2–2% (Critchley, 1930; Baptista, 1963; Dunker and Harris, 1976) (Fig. 25.13).

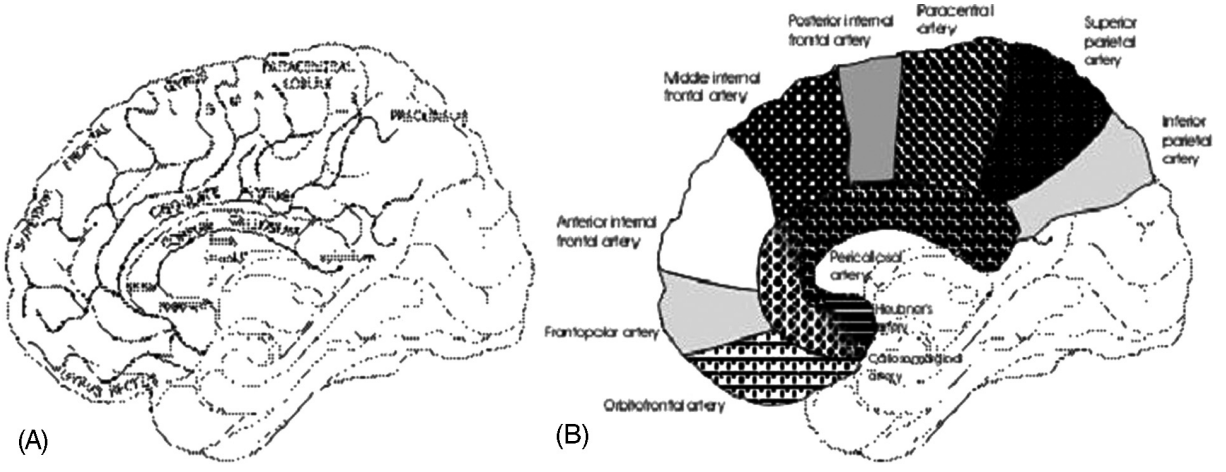

Fig. 25.12. Schematic representations of anatomy (A) and superficial and deep branches of anterior cerebral artery (B). SMA = supplemetary motor area.

Table 25.5

Frequency, site of origin, and area of supply for cortical branches

Cortical arteries	Presence (%)	Site of origin A2	A3	A4	A5	CM	Areas of supply
Oribitofrontal	100	100	—	—	—	—	GR, OB, OT, FL (medial orbital surface)
Frontopolar	100	90	—	—	—	10	FP (medial, lateral surface)
Anterior internal frontal	86	14	48	—	—	24	Anterior third of SFG
Middle internal frontal	90	2	42	4	—	42	Middle third of SFG
Posterior internal frontal	76	—	24	24	—	28	Posterior third of SFG, part of CG
Paracentral	90	—	18	32	14	26	Paracentral lobule
Superior parietal	78	—	—	10	50	18	Superior precuneus
Inferior parietal	64	—	—	10	52	1	Inferior precuneus, adjacent cuneus

CM = callosomarginal artery; CG = cingulated gyrus; FL = frontal lobe; FP = frontal pole; GR = gyrus rectus; OB = olfactory bulb; OT = olfactory tractus; SFG = superior frontal gyrus (Perlmutter and Rhoton, 1978).

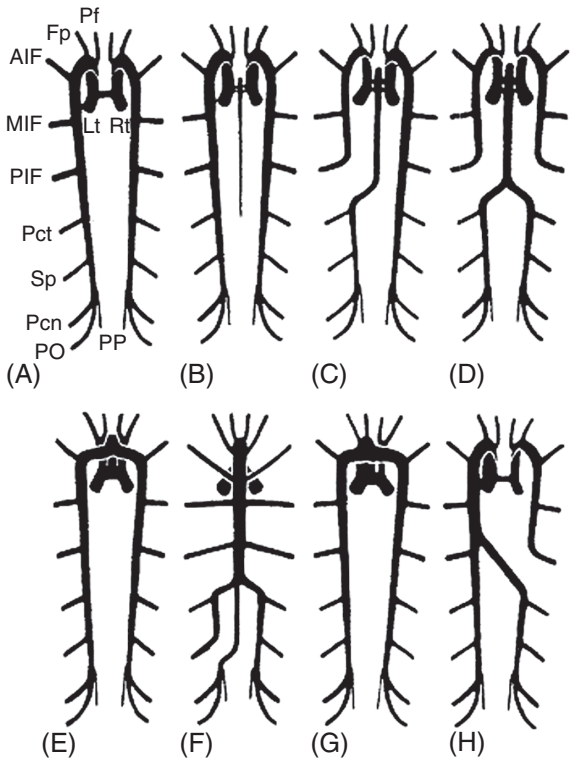

Fig. 25.13. Variations in the anterior cerebral artery including patterns without (A) and with (B) a medial artery of the corpus callosum and variously developed accessory (C–E), unpaired (F), and bihemispheric lateral arteries (G and H). AIF = anterior internal frontal; Fp = frontopolar; MIF = middle internal frontal; Pcn = precuneal; Pct = paracentral; Pf = prefrontal (orbito-frontal); PIF = posterior internal frontal; PO = parieto-occipital; PP = posterior pericallosal; Sp = superior parietal. From Baptista (1963).

A large callosal artery with as large a diameter as the pericallosal artery of the corpus callosum arises from the AComA in 1.5–2.0% of brains. This artery is also called the median artery of the corpus callosum, the arteria termatica of Wilder, or the median ACA.

In normal humans, an ACA may originate from the primitive olfactory artery, eventually becoming the dominant vessel. The infraoptic ACA is a remnant of the embryonic primitive maxillary artery, present in 3- to 4-mm embryos as an ICA branch, that normally becomes a cavernous carotid branch, the inferior hypophyseal artery.

During fetal life, there is gradual transition from one to two ACAs. An azygous or unpaired ACA arising from proximal union of the ACAs without an AComA occurs in 0.5–5% of adult brains. Azygous ACAs are associated with a variety of other anomalies, including vascular malformations, saccular aneurysms, meningomyelocele, hydranencephaly, and holoprosencephaly (Foix and Hillemand, 1925; Lazorthes et al., 1956; Van der Eecken, 1961).

A large variability occurs in the boundaries between the anterior, middle, and posterior cerebral arteries. In subjects with the most extensive ACA distribution, the medial as well as the convexity of the sensorimotor cortex is supplied by the ACA. In those with the least extensive ACA distribution, the ACA supplies little or none of the primary sensorimotor cortex, even medially (Van der Zwan et al., 1992).

25.2.4. Cause of stroke

Isolated infarction of the ACA is uncommon—the frequency in the literature varies from 0.6% to 3% of all

ischemic stroke cases in the registries (Kazui et al., 1987, 1993; Bogousslavsky and Regli, 1990a; Kumral et al., 1998). Most of the patients with ACA infarction frequently also have lesions in the MCA territory. Unilateral or bilateral infarction caused by vasospasm following rupture of saccular aneurysms of the ACA or the anterior communicating artery (AComA) is estimated to be similar to the incidence of ischemic stroke, on the basis of the epidemiological data concerning the rate of symptomatic vasospasm following ruptured aneurysms (Table 25.6).

Patients with isolated ACA territory infarcts often have ICA atherosclerosis and a source of cardioembolism (atrial fibrillation, recent myocardial infarction), but most of these patients presented atherosclerotic disease without significant stenosis (Castaigne et al., 1975; Gacs et al., 1983; Kazui et al., 1987; Kazui et al., 1993;). It has been reported that simultaneous infarcts in the MCA and ACA territories are more often associated with ICA atherosclerosis than with primary stenosis or thrombosis of the ACA itself. In some cases, without an obvious cause of stroke, vascular risk factors for atherosclerosis are common. In situ thrombosis of the ACA without significant carotid stenosis is more common in Asian populations (Bogousslavsky and Regli, 1990, Kazui et al., 1993, Kumral et al., 2002). (Table 25.6)

Embolization to the ACA may occur following some unusual hemodynamic circumstances, such as unilateral ICA occlusion, an azygous ACA, or a hypoplastic A1 segment. In these cases, emboli originating from the heart, aorta, or carotid arteries are prone to reach the distal ACAs through the proximal ACA when there is increased blood flow. Bilateral ICA and ACA stenosis, or a small-caliber AComA, which could limit distal perfusion, can cause unilateral or bilateral ACA territory infarction (Castaigne et al., 1975; Rodda, 1986). The size of the lesion depends on the anatomical patterns of the anterior circle of Willis, the location of arterial boundary zones, and the site of occlusion.

Other causes of ACA territory ischemia are ICA dissection or dissecting aneurysm of the ACA affecting proximal and distal segments, producing both infarction and subarachnoid hemorrhage, and occur either after head trauma or spontaneously. Other reported causes in case reports of ACA territory infarction include fibromuscular dysplasia, sickle cell anemia, isolated angiitis, Wegener's granulomatosis, alcohol intoxication, disseminated intravascular coagulation, arteritis secondary to neurocysticercosis and tuberculous meningitis, radiation vasculitis 19 years after cranial irradiation for acute lymphoblastic leukemia, dolichoectasia involving the anterior and middle cerebral arteries, and unknown factors causing reversible segmental vasoconstriction and vasodilatation (Castaigne et al., 1975; Swanson, 1987; Call et al., 1988, Bogousslavsky and Regli, 1990; Kazui and Sawada, 1993, Kumral et al., 2002).

Table 25.6

Causes of infarction in the territory of anterior cerebral artery

Large-artery disease
Local atherothrombosis of ACA
Artery-to-artery embolism from ICA or ACA
Propagation from ICA occlusion
Cardioembolism
Lacunar infarction in the territory of branch arteries
Cerebral aneurysm
Vasospasm following rupture of aneurysm
Surgery related
Artery-to-artery embolism from unruptured aneurysm
Others
Fibromuscular dysplasia
Dissection
Wegener's granulomatosis
Isolated angiitis
Sickle-cell anemia
Reversible segmental vasoconstriction and vasodilatation
Transfalcial herniation
Arteritis following neurocysticercosis and tuberculous meningitis
Dolichoectesia of anterior cerebral arteries

25.2.5. Symptoms and signs

The specific and varied clinical features of ACA territory infarction may differentiate them from other territorial infarctions. The clinical picture depends on the lesion-side of ACA involvement (Table 25.7).

25.2.5.1. Consciousness and behavioral disturbances

Disorientation, confusion, and memory impairment (mild to severe) may occur following unilateral ACA infarction. Persistent mutism or consciousness disturbances usually occur in large, bilateral ACA territory involvement (Cambier and Dehen, 1973; Laplane et al., 1981; Brust et al., 2001). Retrograde and anterograde amnesia after AComA aneurysm rupture may be mild or severe. A patient with bilateral lesions of both medial frontal lobes plus the right inferior temporal lobe will have impaired recognition of presented words and pictures, and spontaneous recall. The responsible structures that have been implicated in the amnestic syndrome include midline and basal forebrain supplied by the perforating branches of the AComA. Persistent denial or spontaneous confabulation

associated with amnesia may appear in cases with additional mesial frontal damage (Freemon, 1971).

Involvement of the proximal ACA, especially branches originating from the A1 segment or the AComA, can produce a variety of emotional and behavioral disturbances. Anxiety, fear, talkativeness and agitation have occurred with bradykinesia, grasp reflexes, or suck reflexes. Damage of the hypothalamus and other limbic structures may develop unprovoked agitation and screaming following consciousness disturbances. Apathy, poor motivation, and initiative loss may predictably follow dorsolateral frontal infarction, but orbitofrontal lesions cause disinhibited behavior (Kazui et al., 1987; Bogousslavsky and Regli, 1990). Depression may follow left caudate infarction. Left hemineglect with difficulty dressing, drawing, and copying has been seen to occur after infarction of the caudate and anterior limb of the internal capsule (Caplan, 1990).

25.2.5.2. Motor and sensory deficits

Weakness and sensory loss are among the most frequent clinical pictures in those with ACA occlusion, resulting from infarction of the paracentral lobule. Classically, involvement of the cortical branch territory usually results in weakness of the foot and leg and to a lesser degree, paresis of the arm, with the face and tongue largely spared (Critchley, 1930; Bogousslavsky and Regli, 1987a). Lower extremity weakness is severe distally. An extensor plantar response is frequently present with initially flaccid or spastic tendon reflexes. The limb weakness is most severe distally for the following reasons: the proximal leg is represented on the primary sensorimotor cortex either superiorly on the medial hemisphere or on the high convexity with richer collateral arteries from the MCA, and proximal muscles have substantial representation in the ipsilateral hemisphere. In patients with lesions extending to the upper convexity, proximal arm weakness or slowness and clumsiness may predominate. Some patients develop crural monoplegia (Wilson, 1923). Patients with infarction extending deeply may have weakness of the same degree in both arm and leg, or hemiparesis with brachial predominance. In a series of 48 patients with isolated ACA territory infarction, all of those with unilateral infarction developed limb weakness contralateral to the infarction side, crural monoparesis in 4%, hemiparesis with crural predominance in 58%, and hemiparesis of the same degree in the arm and leg in 33% (Table 25.7.) (Kumral et al., 2002). Pure motor hemiparesis or homolateral ataxia and crural hemiparesis, may develop following distal ACA occlusion (Weisberg 1978, Bogousslavsky et al., 1992) (Fig. 25.14).

Occlusion of the recurrent artery of Heubner and perforating branches originating from the most proximal portion of the A1 segment, which supply the genu and contiguous posterior limb of the internal capsule, can cause hemiparesis with faciobrachial predominance (Dunker and Harris, 1976). Dysarthria may accompany faciobrachial weakness after unilateral infarction of either the left or right anterior limb of the internal capsule or caudate nucleus (Caplan et al., 1990; Kumral et al., 2002). Bilateral involvement of the ACA territories may result in paraparesis with or without sensory deficits, due to occlusion of an ACA in the presence of a hypoplastic A1 segment or an azygous distal ACA and following rupture of ACA/AComA aneurysm (Swanson et al., 1987; Ferbert and Thorn, 1992; Borggreve et al., 1994; Minagar and David, 1999). When the weakness is stutteringly progressive, spinal cord or basilar artery disease may be erroneously suspected. In infantile hydrocephalus, pulsatile flow in the ACAs may decrease and result in secondary ACA ischemia, which can cause the lower extremity spasticity and gait disturbance seen in adult normal pressure hydrocephalus (Hill and Volpe, 1982; Bogousslavsky & Melo, 2001).

The sensory modalities most often affected are discriminative (stereognosis, localization, two-point discrimination) and propriocepive (position sense). Pain and temperature sensation and gross touch are usually mildly decreased. Vibratory loss is variable. Sensory deficits may be found in the affected half of the body, particularly in the lower extremity, and are usually mild or even absent depending on the posterior extent of the ACA and collaterals from the PCA. Isolated sensory deficit is a rare entity in ACA territory infarction and may develop following isolated occlusion of the paracentral branch (Wilson, 1923, Critchley, 1930).

25.2.5.3. Pathological grasp reflex and reaction

The grasp reflex is a flexion–adduction response in the hand or foot digits provoked by a distally moving pressure contact on an area of the palmar aspect of the hand (Lhermitte et al., 1907; Chavany et al., 1955). A pathological grasp reflex may result in some patients with unilateral or bilateral ACA territory infarction, and even with involvement of the basal ganglia on the opposite site.

The instinctive grasp reaction is a slower reaction to light stationary touch on the skin of any part of the hand (Seyffarth and Denny-Brown, 1948). The grasp reaction has been considered as an aspect of a total change in behavior toward a compulsive exploration of the environment; foot grasping may make the lower limb seem to be glued to the floor on attempted

Table 25.7

Frequency of clinical findings regarding the site of lesion in 48 patients with isolated ACA territory infarction (Kumral et al., 2002)

	Right ACA infarcts	Left ACA infarcts	Bilateral ACA infarcts
	(n = 16)	(n = 30)	(n = 2)
Acute confusional state	19	7	—
Mutism	13	33	—
Akinetic mutism	—	—	100
Abulia	63	30	—
Motor deficits			
F	—	3	—
FUL	50	60	100
UL	50	27	—
L	—	3	—
Sensorial Disturbances			
FUL	25	27	—
UL	6	20	—
L	13	13	—
Neuropsychological findings			
Dysarthria	6	7	—
Decreased verbal fluency	—	13	—
TMoA	6	40	—
TMxA	—	7	—
Motor hemineglect	19	3	—
Anosognosia	6	—	—
Frontal syndrome	25	40	nd
Ideomotor apraxia	6	10	—
Grasping	13	27	100
Alien hand	6	—	—
Utilization behavior	—	—	50
Depressive affect	25	7	—
Urinary incontinence	13	33	100
Fecal incontinence	—	3	50

Values are percentage of column.
nd = neuropsychological tests could not be performed.
F = face; U = upper limb; L = lower limb; TMoA = transcortical motor aphasia; TMxA = transcortical mixed aphasia.

walking. The magnet reaction, trap reaction or instinctive groping of the contralateral hand, which can be partially inhibited by the patients' intention, are subtypes of this grasp reaction. Patients may also display sucking and biting, ansaugen (a movement of the lips and tongue toward stimulation of the skin near the lower lip), catalepsy, and tonic innervation (amorphous movements of a pseudospontaneous character) on attempted voluntary action of the affected limbs (Kumral et al., 2002). In the acute phase of stroke, ACA or MCA territory infarcts may cause hyperkinetic motor behaviors (including rhythmic movement of the fingers, flexion and extension of the thigh, head and eye movements, grimacing and chewing) on the contralateral, nonparalyzed side, suggesting an active process induced by disinhibition in order to establish new compensatory pathways (Ghika et al., 1995). Involvement of the medial frontal lobe, including the superior frontal and cingulated gyri, with or without an anterior callosal lesion, may result in an instinctive grasp reflex (Seyffarth and Denny-Brown, 1948).

25.2.5.4. Sphincter dysfunction and autonomic disorders

Urinary (or less frequently, fecal) incontinence has been reported as a classical symptom of either unilateral or bilateral ACA occlusion, although the reported frequency is relatively low. Involvement of the paracentral lobule or the superior medial frontal lobe (especially the midportion of the superior frontal gyrus, the cingulate, and the white matter in between)

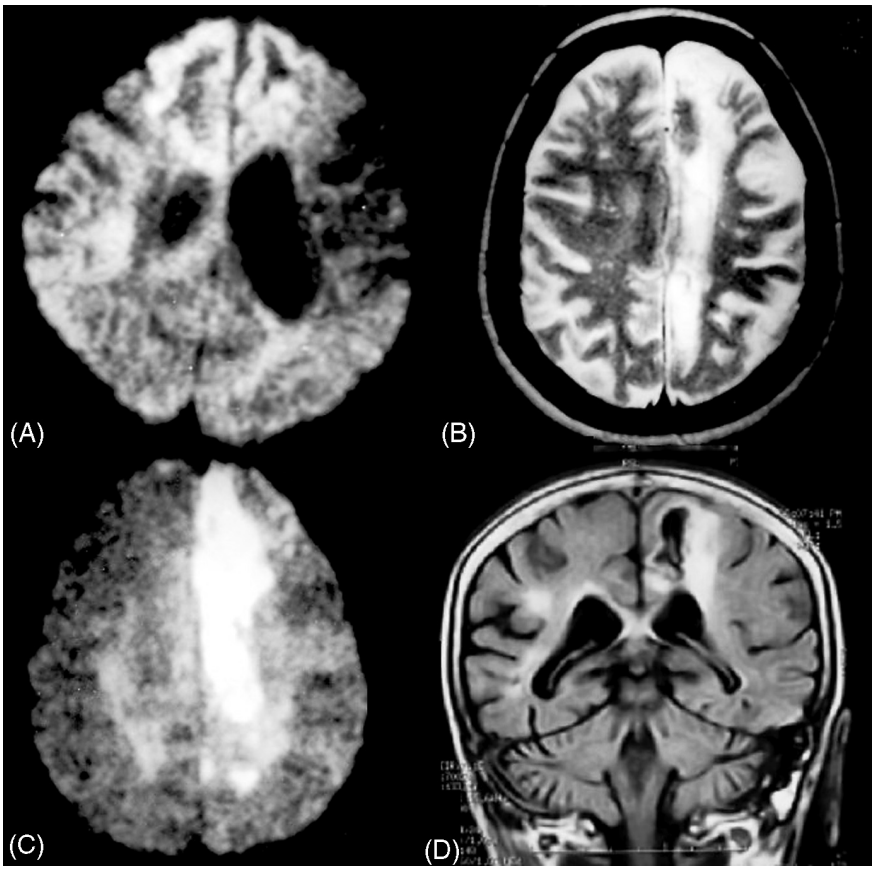

Fig. 25.14. (A) Diffusion-weighted image demonstrates acute bilateral ischemic changes in the territory of the anterior cerebral artery. The patient had an old left ischemic area in the MCA territory. (B) Axial T_2-weighted image shows extensive anterior cerebral artery infarction. (C) Diffusion-weighted image demonstrating acute lesion in the territory of anterior cerebral artery. (D) coronal T_1-weighted image showing chronic infarct in the territory of ACA.

is a likely cause (Wilson, 1923; Webster et al., 1960; Andrew and Nathan, 1964).

Cardiorespiratory alterations are common after stroke, but are uncommon in patients with ACA occlusion, whether or not limbic structures are damaged (Lloyd, 1979). Infarction of the hypothalamus, cingulate gyrus, and the limbic areas after ACA occlusion may cause these changes. Human and animal cingulated stimulation can produce hypertension or hypotension, altered respiration, respiratory or cardiac arrest, papillary dilatation, and piloerection. After surgical occlusion of a proximal ACA for AComA aneurysm rupture, diabetes insipidus and gastrointestinal bleeding have been blamed on damage caused by anterior hypothalamic infarction.

25.2.5.5. Behavioral and psychomotor disorders

Consciousness and behavioral signs such as prolonged mutism, acute confusional state and abulia may be seen at stroke onset (Sussman et al., 1983). Coma may develop in cases with bilateral proximal ACA occlusion, especially in those with subarachnoid hemorrhage and vasospasm (Freemon et al., 1971). Coma requires either bihemispheric or ascending reticular activating system lesions (Brodal, 1981). Patients in a coma following ACA occlusion either had brain damage not restricted to one hemisphere, or were mute or akinetic, and may be more alert than they seemed.

Akinetic mutism is a state of limited verbal and motor responsiveness to the environment in those without paralysis and coma (patients may have open eyes and brief movements). Speech and agitation to unpleasant stimuli may develop in lesions involving the anteromedial lobes. Patients look apathetic, indifferent, detached, and frozen. The eyes of these patients are open and follow objects, and they are more alert than those with mesencephalic or thalamic lesions. The patients may also make brief, monosyllabic, but appropriate response to questions. In these patients solicited communication is usually retained but spontaneous verbal communication is frequently absent (De Reuck et al., 1982). "Abulia" is a term that defines a mild-to-severe spectrum of decreased

spontaneous speech and spontaneous movement, latency in responding to verbal and stimuli, and impersistence in responses and requires. Often, the answers are emotionally flat, late, or incomplete. Bilateral lesions involving the bilateral cingulated gyrus, medial frontal lobe, supplementary motor area (SMA), and the caudate nucleus may produce persistent abulia. Unilateral ACA lesions produce transient abulia, lasting from a few days to a week, often associated with contralateral motor neglect. Motor neglect must be viewed as unilateral abulia. Following abulia, patients may show an inability to walk despite normal strength and disinclination to move the contralateral arm and leg that can be considered as motor neglect. Damage of the medial premotor area, which is responsible for supramotor programming, has been implicated in clinical and experimental studies. Patients with abulia and motor neglect frequently show relative preservation of reflex (externally stimulated) movements, in contrast to willed and anticipated movements.

In the recovery phase, signs may become more subtle, such as difficulty with sequential movements involving different joints or coordinating the movement of both arms. Lesions of the SMA can cause an inability to reproduce rhythms from memory and to perceive as separate two successive tactile stimuli. Moreover, lesions of the mesial frontal lobe may produce psychiatric symptoms, such as euphoria, paralogia or witzelsucht, and emotional lability.

Abulia and alternating restlessness and hyperactivity without abulia, anxiety, or agitation are reported in patients with unilateral caudate infarction. Patients with left-sided caudate infarction have shown a high frequency of severe depression (Starkstein et al., 1988). These paradoxal behavioral manifestations may result from damage to the dorsolateral caudate (which connects to the dorsolateral frontal lobe) and disinhibition from damage to the ventromedial caudate (which connects to orbitofrontal areas) (Mendez et al., 1989).

25.2.5.6. Language disorders

As mentioned before, muteness is frequently present following acute left or right ACA territory infarction. Reduction of spontaneous verbal expression, global psychomotor bradykinesia or muteness are manifestations of abulia. In such patients, comprehension of spoken speech may be untestable. Most patients with unilateral lesions have a tendency to speak in whispers. Some reports have described true impairment of speech comprehension, word-finding difficulty, alexia, and phonemic or verbal paraphasias on spontaneous speech, reading aloud, or writing (Alexander and Schmitt, 1980; Bogousslavsky and Regli, 1987b). Some authors have emphasized the absence of true paraphasias. Other authors have described impairment of spontaneous speech with normal repetition and sometimes echolalia, considered as transcortical motor aphasia. Echolalia and palilalia can also occur in patients without other evidence of aphasia. Patients with transcortical aphasia (or Luria's dynamic aphasia) have a strikingly greater impairment of list naming than of naming to confrontation and speech initiation impairment, especially in attempts to narrate stories or describe complex pictures. This is probably the result of damage to the SMA, and with a few exceptions, the infarct is likely to have affected the language-dominant hemisphere (Ross, 1980; Brust et al., 1998). Transcortical mixed aphasia presenting with normal repetition but poor comprehension and nonfluent speech may result from infarction of both medial frontal and medial parietal lobes; mirror writing may be found in some cases (Bogousslavsky, 1987b; Chan and Ross, 1988). Speech disturbance was also reported in some cases with right ACA territory infarction, specifically bradykinesia, speech limited to short answers to questions, tendency to echolalia, and impaired naming and comprehension of spoken language (Brust et al., 1982).

Most authors, when considering these language disorders, attribute them to involvement of the SMA on the medial surface of the frontal lobe, anterior to the paracentral lobule, and between the cingulated and superior frontal gyri (Penfield and Welch, 1951; Damasio and Kassel, 1978; Bogousslavsky and Regli 1987b; Iragui, 1990). Stimulation of the SMA on either hemisphere produces bodily postures, repetitive movements, speech and movement arrest, vocalization, intermittently repeated words, syllables, or meaningless combinations of syllables (saccadic vocalization). Rhythmic mouth and jaw movements, and sometimes hesitation or slowed speech, may also occur, suggesting attempted speech or an arrest of other voluntary movements.

Mirror writing is the result of infarction in the left or right SMA sparing the corpus callosum. The SMA is responsible for nonmirror transformation of motor programs originating in the left hemisphere before execution by the primary motor area in the right hemisphere. Acquired stuttering can result from lesions in right, left, or bilateral frontal areas, or in the anterior corpus callosum, without any other language deficit. Primary dyscalculia has been reported after infarction in the territory of the left ACA.

25.2.5.7. Callosal disconnection syndrome

Distinct syndromes of callosal disconnection, ideomotor apraxia, agraphia, and tactile anomia, may occur in the left hand of patients with ACA occlusion or in

right-handed patients with callosal tumors (Brion and Jedynak, 1972; Bogen, 1979). Patients with a disconnection syndrome display left-handed agraphia, writing incorrectly both spontaneously and to dictation, and erroneously writing calculations with the left hand. They cannot name objects, letters, or numbers with their left hand placed out of sight, but can identify them afterwards with the left hand by pointing to them. They have difficulty executing verbal commands with the left hand (e.g., show how to comb out the hair, salute the examiner, draw a circle). Their right hand can write normally but their left hand may incorrectly copy writing. Either hand can imitate the examiner's movements or manipulate objects (Geschwind and Kaplan, 1962).

Inability to perform learned skilled movements with the left hand following verbal commands (e.g., brushing one's teeth, combing one's hair, saluting,) in contrast with correct and flawless performance with the right hand is referred to as unilateral ideomotor apraxia. Most patients with ACA infarctions have shown a more or less impaired ability to imitate and use actual objects with the left hand. Some authors have suggested that space–time and visuomotor engrams are localized in the left hemisphere, and that callosal apraxia with impaired object use and imitation is the result of disconnection between these motor engrams and the right hemisphere (Goldberg et al., 1981; Watson and Heilman, 1983). In left-handed patients, dominance of language and skilled motor acts seem to be in different hemispheres, and this is supported by some observation. The main anatomical part of the corpus callosum is the body for impaired imitation and object use, at which the primary pathway for praxis from the left hemisphere to the right may be disrupted.

In those with left-hand agraphia having normal linguistic and writing ability, even with or without a paresis or grasp reflex, there is a tendency to write unintelligible letters, incorrect words, unrecognizable scrawls, added and missed strokes, substitutions or perseverations to dictation or in spontaneous writing (Geschwind and Kaplan, 1962; Yamadori et al., 1980). They may have errors in typing and forming block letters. In a Japanese patient with occlusion of the left pericallosal artery, left unilateral agraphia for kanji (the morphograms) but not for kana (the syllabograms) was developed, suggesting that for these two types of linguistic information, different neural pathways are used at the level of the posterior body of the corpus callosum. (Kawamura et al., 1989). Occlusion of the ACA extending around the splenium of the corpus callosum can produce pure alexia in the left visual field, and visual anomic or agnostic deficits (Watson and Heilman, 1983; Goldenberg et al., 1985).

In a patient with left ACA territory infarction there was difficulty naming her left fingers and moving her named left fingers. She could also not point to her own body parts with left hand. In this case, the left cerebral hemisphere organizing body schema was disconnected from her right hemisphere as a consequence of the callosal infarction (Nagumo and Yamadori, 1995). Unilateral tactile anomia is an impairment of the ability to name subjects placed in the left hand, but such a patient can correctly and promptly name objects in the right hand. The patient is able to indicate the correct objects with eyes closed when an object is placed in the left hand and then removed and placed on a multiple choice array, demonstrating intact stereognostic capacity. Tactile anomia of the left hand has been associated with unilateral agraphia, and results from a lesion in the posterior part of the callosal body.

Alexia in the left hemifield, anomia for objects placed in the left hand, left-handed apraxia and agraphia, and bilateral pseudoneglect, developed in a patient with bilateral ACA vasospasm due to colloid hemorrhage (Heilman et al., 1984). This patient displayed left hemineglect with the right hand in the left hemispace and right hemineglect with the left hand in the right hemispace on the visual or tactile line bisection test (Kashiwagi et al., 1990; Kumral et al., 1995). Disconnection of the hemisphere important for directing attention–intention into the contralateral hemispace from the hemisphere important for controlling sensory-motor processing of the limb is a likely cause. The damage was located in the body of the corpus callosum, probably disrupting communication between the cerebral hemisphere, which is important for directing the intent to attend to the contralateral space. On the other hand, left hemispatial neglect confined to right-hand and verbal responses in tasks, occurred in a patient with infarction of the posterior genu and whole trunk of the corpus callosum plus left medial frontal and temporo-occipital lobes. This disconnection syndrome was consistent with the hypothesis that the left hemisphere was concerned with attending to the contralateral hemispace, and the right hemisphere was specialized to both sides of space. This type of neglect does not seem to develop with lesions restricted to the corpus callosum but also requires additional damage involving the medial frontal lobe that disrupts transmission through extracallosal commissures (Goldenberg, 1985; Trojano et al., 1993).

Optic ataxia (or crossed visuomotor ataxia) is an inability to reach and grasp an object placed in the peripheral visual field of the opposite site. Damage in the dorsal aspect of the posterior callosum may result in optic ataxia, by blocking transmission in the

visuomotor pathway. A crossed avoiding reaction has been reported in patients with a lesion in the genu and body of the corpus callosum and the left cingulate gyrus (Nagumo et al., 1993). These patients were unable to move the left hand when they intended to grasp the stimulus placed in the right hemispace.

25.2.5.8. Alien hand and dissociative movements

Some patients with ACA occlusion and left-sided apraxia do not perform well on bimanual tasks, and sometimes the two hands seem to be fighting each other (Bogen, 1979). Alien hand ("le signe de la main étrangère") was described as a feeling without defect in deep sensation but the left hand does not belong to the patient when it is held by the right hand behind the back (Banks, 1989). The term "alien hand sign" includes a spectrum of dissociative movements between the right and left hands which are developed as a result of damage of the corpus callosum and medial frontal lobe, or both (Goldberg et al., 1981). The term "motor perseveration" denotes spontaneously occurring, simple, repetitive, stereotyped movements of the hand , such as rubbing the thumb and index finger or smoothing or patting bedclothes (Shahani et al., 1970). Motor perseveration is often associated with an instinctive grasping reaction and a grasp reflex which results from a lesion of the medial frontal lobe contralateral to the affected hand.

Patient with lesion in the left ACA territory could not help grasping familiar object (such as a toothbrush or pen) placed before her and using it appropriately with her right hand. These movements could be restrained by the patient's left hand and not by the examiner's verbal command. The mechanism of this compulsive manipulation is likely a kind of release phenomenon of learned praxis following damage to the left mesial frontal lobe, SMA and cingulated gyrus, and genu of the corpus callosum (Mori and Yamadori, 1982). Utilization behavior is also a similar compulsive phenomenon characterized by use of familiar objects by both hands in front of the patient, but this syndrome is different because of its lack of compulsiveness, its bilateral hand involvement, and the causative lesions in different locations (Lhermitte, 1983). Purposeless movements of either the right or left hand, such as drifting upward, keeping it tucked within the axilla, or grasping one's throat, have been reported in some cases with lesions in the medial lobe and the genu and body of the corpus callosum contralateral to abnormal movements (McNabb et al., 1988; Banks et al., 1989).

Diagnostic dsypraxia has been described in a patient with a dissociative movement in which one of the patient's hands acts at cross-purposes to the other, such as putting on one's object with the right hand and followed by pulling them off with the left hand. This type of voluntary activity is triggered by the movement of the other hand, and is invariably accompanied with a disconnection syndrome. This type of movement, so-called "anarchic hand," has been described in a patient with callosal hemorrhage involving the genu and body (Kumral, 2001). The lesion of the body of the corpus callosum is likely cause of these dissociative movements (Akelaitis, 1945; Tanaka et al., 1990).

25.3. Middle cerebral artery

25.3.1. Anatomy

The middle cerebral artery (MCA) is the larger of the two terminal branches of the internal carotid artery (ICA). Two approaches are usually used for the anatomical description of the MCA. The first is a "functional branching approach," which uses classical anatomic terminology. This method is more useful for understanding stroke mechanisms and describing the clinical syndromes of occlusion of the cortical branches.

The MCA generally arises as a single horizontal trunk (the MCA stem). The length (from 18 to 46 mm, average 30 mm) and diameter (from 2.4 to 4.6 mm, average 3.9 mm) of the MCA stem are variable (Rhoton, 2002). The MCA stem gives off a series of perforating branches referred to as lenticulostriate arteries (LSA). The number of LSAs varies from 1 to 21 (average 10) per hemisphere. They supply the putamen and pallidum or the lentiform nucleus, internal capsule (the upper part of the anterior limb and genu, and the anterior part of the posterior limb), and caudate nucleus (the head and the body). The LSAs are terminal arteries without any functional anastomoses with the superficial (pial or medullary) branches, as well as between themselves (Marinkovic et al., 1985; Marinkovic et al., 1996).

After the lenticulostriate branches, the MCA generally bifurcates, forming superior and inferior divisions or trunks (Fig. 25.15A). In approximately 10%, the MCA trifurcates into the inferior, middle, and superior divisions (Fig. 25.15B); and in another 10% it directly gives off the small cortical branches without formation of major divisions and is known as ramification pattern (Fig. 25.15C) (Gibo et al., 1981).

There are twelve cortical branches originating from the MCA (Fig. 25.15). These branches supply the lateral surface of the hemispheres including the frontal and parietal lobes, and the superior portion of the temporal lobe, white matter, claustrum, and the extreme capsule. Separate cortical territories of the 12 branches of the MCA are displayed in Fig. 25.16. The first three

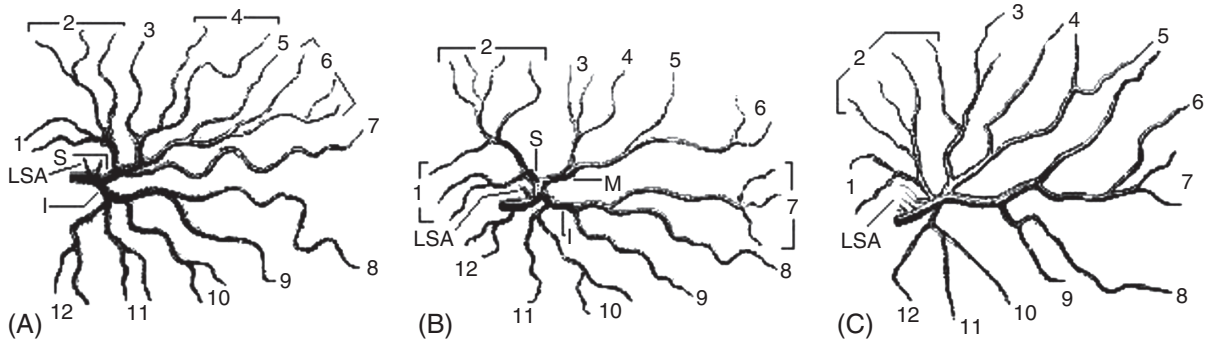

Fig. 25.15. Branching patterns of the MCA. (A) Bifurcation. (B) Trifurcation. (C) Ramification. LSA = lenticulostriate arteries; I = inferior division; S = superior division; M = middle division; 1 = orbitofrontal artery; 2 = prefrontal artery; 3 = precentral artery; 4 = central artery; 5 = anterior parietal artery; 6 = posterior parietal artery; 7 = angular artery; 8 = temporo-occipital artery; 9 = temporopolar artery; 10 = anterior temporal artery; 11 = posterior temporal artery; 12 = middle temporal artery. Adapted from Gibo et al. (1981).

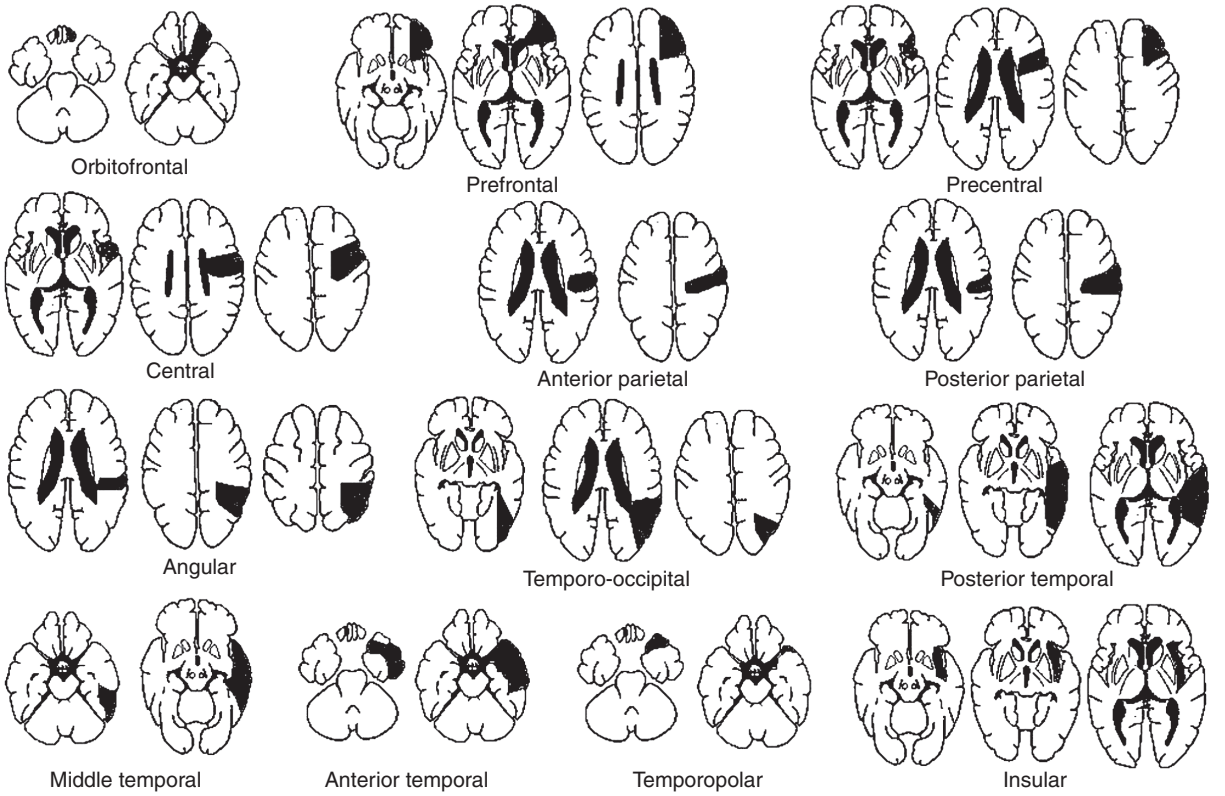

Fig. 25.16. Schematic representation of the territories of the cortical branches of the MCA. Adapted from Neau and Bogousslavsky (1998) and Bories et al. (1985).

branches, the orbitofrontal artery, prefrontal artery, and precentral artery, invariably originate from the superior division when the MCA bi- or trifurcates. The orbitofrontal artery supplies the orbital portion of the middle and inferior frontal gyri, and inferior pars orbitalis. The prefrontal artery supplies the superior pars orbitalis, pars triangularis, anterior pars opercularis and the middle frontal gyrus. The precentral artery supplies the posterior pars opercularis, posterior middle frontal gyrus, anterior and middle parts of the central gyrus. The central artery, also known as the rolandic artery, arises from the superior division in

the bifurcation pattern, and from the middle division in the trifurcation pattern. Its territory includes the posterior precentral gyrus and the anterior half of the post-central gyrus. The anterior parietal artery originates from either the superior (or middle if the MCA trifurcates) or inferior division. The posterior post-central gyrus, parasagittal portion of central sulcus, and anterior portions of the inferior and superior parietal lobules are nourished by this branch. The posterior parietal artery arises from either the superior or inferior division in a bifurcation pattern. It supplies the posterior parts of the superior and inferior parietal lobules including the supramarginal gyrus. The angular artery usually supplies the posterior portions of the superior temporal gyrus. It also supplies the supramarginal and angular gyri, and the superior part of the lateral occipital gyrus. The source of the angular artery is either the superior or inferior division in the bifurcation pattern. The temporo-occipital artery usually supplies the inferior part of the lateral occipital gyrus, posterior half of superior temporal gyrus, and the most posterior portions of the middle and inferior temporal gyri. The inferior division is usually the source of this artery. In a tripodic branching pattern of the MCA, the precentral, posterior parietal, angular, and temporooccipital branches may also arise, albeit less often, from the middle division. The last four branches of the MCA, the temporo-polar artery and anterior, posterior, and middle temporal arteries emerge generally from the inferior division in divisional patterns. The temporo-polar artery supplies anterior portions of the superior, middle, and inferior temporal gyri. The middle temporal artery supplies the superior temporal gyrus, the middle part of the middle temporal gyrus, and the middle and posterior parts of inferior temporal gyrus. The temporo-polar artery supplies anterior poles of the superior, middle, and inferior temporal gyri, and the posterior temporal artery supplies the middle and posterior parts of superior temporal gyrus, the posterior third of the middle temporal gyrus, and the extreme posterior part of inferior temporal gyrus (Neau and Bogousslavsky, 1998; Rhoton, 2002). It is important to note that these cortical branches give no significant branches to one another. They terminate in a complex vascular network, where there are anastomoses with the pial vessels of PCA and ACA (Duvernoy et al., 1981).

The superficial branches of the MCA supply most of the hemispheral white matter through the medullary or superficial perforating arteries (Fig. 25.17), which penetrate the centrum semiovale and course toward the upper part of the lateral ventricles (De Reuck, 1971). These medullary branches usually have single territories, do not anastomose to one another, and tend to form a borderzone with the LSA and AChA at the deeper part of the corona radiata. It has been emphasized that these borderzones cannot be watersheds because of the absence of actual anastomoses between the medullary arteries and the LSAs or the branches of the AChA. However, the borderzone between the pial vessels is a watershed because two or more channels connect each other (Bogousslavsky and Regli, 1992).

The other approach, known as "the segmental approach," analyzes branches of the MCA in relation

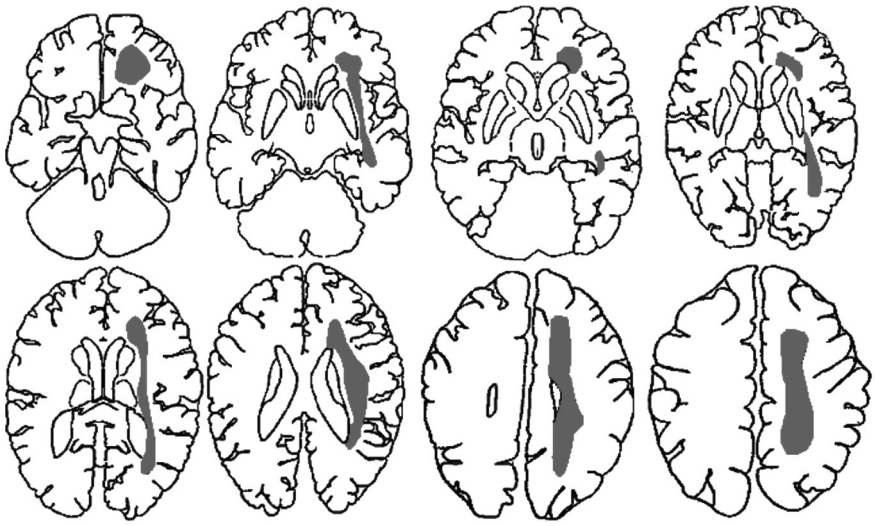

Fig. 25.17. Schematic representation of the territory supplied by the medullary arteries. Reproduced with permission from Bogousslavsky and Caplan (2001).

to brain landmarks dividing the artery into segments. This approach is applied most often for angiographic purposes. The MCA is divided into four segments: M1 (horizontal or sphenoidal), M2 (insular), M3 (opercular), and M4 (cortical) (Fig. 25.18). The M1 segment begins at the origin of MCA at the intracranial bifurcation of the ICA and extends laterally within the Sylvian fissure. This segment terminates at the site of a 90° turn, the genu of the MCA, located at the junction of the sphenoidal and operculo-insular compartments of the Sylvian fissure. It contains the stem and the first several centimeters of the divisions after bifurcation. It is subdivided into prebifurcation and post-bifurcation portions. Most of the LSAs arise from this segment. The M2 segment runs along the insula and provides most of the cortical branches. This segment extends from the genu to the circular sulcus of the insula. The M3 segment follows the operculum superior to the insula. After two 180° turns, it ends at the surface of the Sylvian fissure. Finally, the M4 segment describes branches of the MCA perfusing nearly all the lateral convexity. They begin at the surface of the Sylvian fissure and extend over the cortical surface of the cerebral hemispheres except for the frontal pole and the posterior rim (Osborn, 1999).

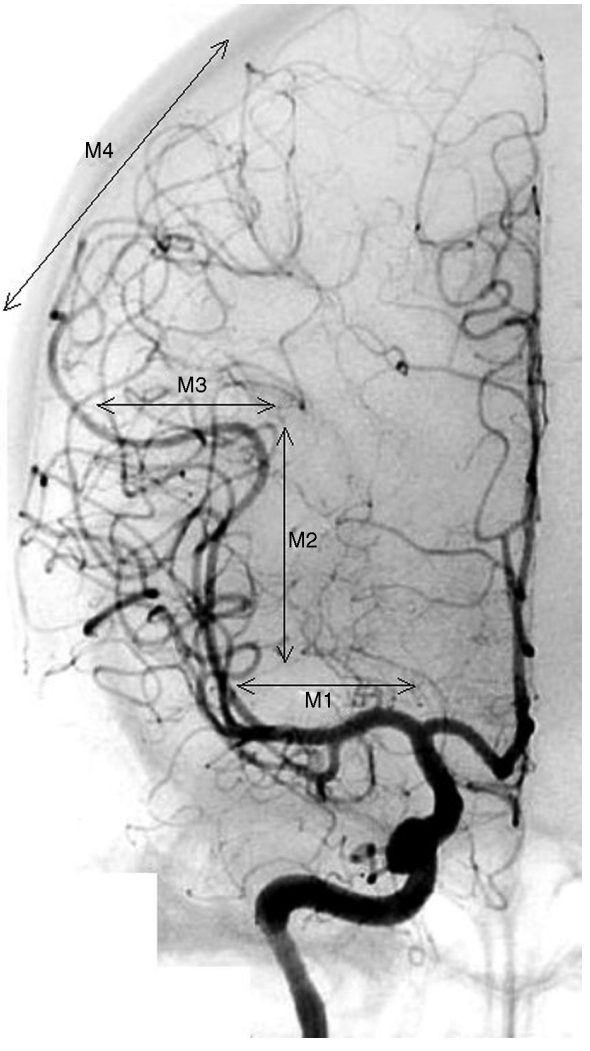

Fig. 25.18. Contrast cerebral angiogram demonstration of the segments of MCA (lateral view). M1 = horizontal; M2 = insular; M3 = opercular; and M4: cortical.

25.3.2. Symptoms and signs

25.3.2.1. Confusion and delirium

Attention and concentration are the ability to keep a consistent flow of cognitive functioning. Confusion is the inability to execute cognitive functions with an inability to think with ordinary clearness, regularity, and rate. Delirium is the term defining confused patients having additionally increased psychomotor activity or perceptual disturbances with a disordered awake–sleep cycle (Lipowski, 1990). The major symptoms of confusion are obvious: the patient lacks interest, is unable to sustain concentration, and feels tired and distractible. If the patient additionally has agitation, hallucinations, and is thrashing about, the diagnosis is delirium (acute confusional state). Delirium can be detected by the confusional assessment method based on DSM-III criteria (Fig. 25.19) (Inouye et al., 1990) and the severity of delirium can be rated by using validated scales such as the Delirium Rating Scale (Fig. 25.20) (Trzepacz et al., 1988) and the organic Brain Syndrome Scale (Gustafson et al., 1993; Sandberg et al., 1999; Ferro et al., 2002).

Stroke is one of the leading causes of conscious disorders from confusion to deep coma. In stroke patients, delirium has been reported in single case reports, small groups of patients, and retrospective studies (Dunne

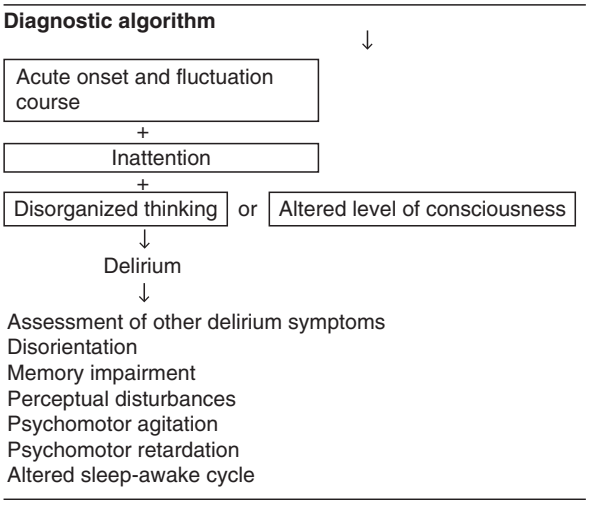

Fig. 25.19. The confusional assessment method.

Delirium Rating scale
1. Temporal onset of symptoms
2. Perceptual disturbances
3. Hallucination type
4. Delusions
5. Psychomotor behavior
6. Cognitive status during formal testing
7. Physical disorder
8. Sleep-awake cycle disturbances
9. Lability of mood
10. Variability of symptoms

Items 1, 2, 3, 4, 5, and 9 are rated 0, 1, or 2; items 6, 8, and 10 are rated 0, 1, 2, 3, or 4; item 7 is rated 0, 1, or 2. Adapted from Trzepacz et al (1987)

Fig. 25.20. Delirium Rating Scale.

et al., 1986; Mori and Yamadori, 1987; Cervero et al., 1990; Nicolai and Lazzarino, 1994; Hénon et al., 1999). In one of the cohort studies, delirium occurred in one-fourth of 202 stroke patients older than 40 years and was related to the occurrence of a confusional state with pre-existing cognitive decline (Hénon et al., 1999). The Oxfordshire Community Stroke project revealed 15% of stroke patients had a reduced level of consciousness during the first days of the event, while 420 (42%) of 991 patients admitted to the Mayo Clinic were recorded as having a reduced level of consciousness (Turney et al., 1984; Warlow et al., 2001b). In a prospective study conducted in 145 stroke patients delirium occurred in 48% of patients (Gustafson et al., 1991).

Focal forms of delirium have been described after strokes in specific locations: (1) uni- or bilateral anterior or dorsomedial thalamic infarcts or hemorrhages; (2) uni- (predominantly left) or bilateral posterior cerebral artery infarcts; (3) bilateral anterior cerebral artery infarcts, mesial or orbital frontal infarcts, or hematomas in the setting of subarachnoid hemorrhage; (4) inferior part of the genu of the internal capsule; (5) caudate infarcts and hemorrhages; (6) right middle cerebral artery infarcts, in particular if there is damage to the frontostriatal region (hypoactive forms) or the middle temporal gyrus (hyperactive forms); and (7) primary intraventricular hemorrhage (Ferro et al., 2002; Trzepacz, 1999). In several clinical stroke studies, patients having lesions in the specifically above mentioned locations did not have delirium or the authors did not use the term delirium (Madureira et al., 1999; Ghika-Schmid and Bogousslavsky, 2000).

Among the ischemic stroke population, a confusional state is mostly seen with right hemispheric superficial lesions, and is less frequent with posterior fossa strokes (Mullally et al., 1982; Dunne et al., 1986; Hénon et al., 1999; Devinsky et al., 1988). Hyperactive agitated patients have lesions mostly in the temporal, occipital, or inferior parietal lobes, and mostly involve the limbic cortex (Bostwick, 2000). Postmortem and clinical studies showed lesions in the right hemisphere and right temporal lobe infarcts (Boudin et al., 1963). Juillet and colleagues also reported that two of four patients showing agitation and confusion had right temporal lobe infarction (Juillet et al., 1964). Mesulam et al. (1976) reported that three patients with confusion and agitation had right temporal, inferior parietal, or inferior frontal lobe lesions due to middle cerebral artery occlusion. In another report, four of ten stroke patients having impaired cognitive functioning had no additional left-sided neurological signs even though all had right temporal lobe lesions (Guard et al., 1979). Many studies reported patients with inattention, hallucinations, and paranoid delusions following probable infarction of the right parietal, frontal, or temporal lobes (Schmidley and Messing, 1984; Price and Mesulam, 1985). Angiographic studies revealed problems in temporal and inferior parietal branches of the inferior division of the right middle cerebral artery (Schmidley and Messing, 1984).

25.3.2.2. Motor deficit

Occlusion of the MCA main stem is nearly always symptomatic, although some young patients with very good cortical collateral supply may have remarkably few symptoms. In most cases, the occlusion occurs in the proximal main stem, thereby involving the LSAs, and consequently there is ischemia of both the deep and superficial territories of the MCA (Warlow et al., 2001c). Typically, this presents as a contralateral hemimotor and sensory deficit, hemianopia, and disturbance of relevant higher cortical functions (e.g., aphasia if in the dominant hemisphere). If the cortical collateral supply from the ACA and PCA is good, ischemia may fall on the subcortical structures, resulting in a striatocapsular infarct, because the thrombus occludes the origins of the deep perforating arteries, which are functional end-arteries. Nevertheless, there is often a degree of cortical ischemia without infarction and consequently the clinical deficits can be very similar. If the occlusion is more distal in the main stem and there is no ischemia in the LSA territory, the leg may be relatively spared, because most fibers will originate in cortical areas usually supplied by the ACA, and will descend medially in the corona radiata adjacent to the lateral ventricle (Ueda et al., 1992).

Hemiparesis with uniform weakness of the hand, foot, shoulder, and hip is the most frequent motor

deficit profile (Herman et al., 1982; Mohr et al., 1984). However, acute stroke presenting as monoparesis is rare, with a pure motor deficit in the arm or leg extending to an isolated facial paresis. In the Lausanne Stroke Registry (1979–2000), 195 (4.1%) of 4,802 patients met the clinical criteria for pure monoparesis involving the face (22%), arm (63%), or leg (15%) (Maeder-Ingvar et al., 2005).

If the patient has a brachial monoparesis, or the weakness affects predominantly the hand and face, it is more likely due to a cortical rather than a subcortical lesion (Boieten and Lodder, 1991; Timsit et al., 1997). When weakness is confined to or predominates in the leg, the lesion is most likely to involve the territory of the anterior cerebral artery (Bogousslavsky and Regli, 1990a). Faciobrachial paresis occurs, in the majority of the patients, due to MCA superficial infarcts (De Freitas et al., 2000). Monoplegia is usually associated with small infarcts of the cortex or centrum ovale (Boiten and Lodder, 1991; Melo et al., 1992b; Bogousslavsky and Regli, 1992). Schneider and Gautier (1994) studied infarct topography of acute stroke patients with leg-predominant weakness. Lesions in the rear portion of the medial part of the precentral gyrus caused predominantly distal, severe, contralateral leg weakness, while the lesions located in the medial part of the premotor cortex, the supplementary motor area and the posterior portion of the medial part of the precentral gyrus caused hemiparesis with predominantly leg paresis contralaterally. Lesions affecting the medial part of the premotor cortex and supplementary motor area but sparing the precentral gyrus cause a contralateral proximal hemiparesis predominating in the leg, with good recovery (Freund & Hummelshein, 1985). The syndrome of hemiplegia caused by an infarct of the entire surface territory of the MCA was characterized by brachial predominance of hemiplegia, rarely involving mainly distal parts (Melo and Bogousslavsky, 2002).

Ischemic stroke patients with hemiparesis sparing the legs usually have damage in the motor cortex supplied by the MCA, superficial branches of the MCA, or the LSAs (Melo and Bogousslavsky, 2002). De Freitas et al. (2000) studied 895 stroke patients with paresis sparing the leg (73% faciobrachial, 21% brachial, and 6% facial) and showed that they nearly 50% of patients had a superficial infarct of the superficial branches of the MCA. Bilateral anterior watershed infarcts (between the ACA and MCA) limited to the cortex may produce bibrachial paralysis (“man in the barrel”), because the junction of ACA and MCA territories is at the level of the arm–shoulder representation in the motor strip (Melo and Bogousslavsky, 2002).

25.3.2.3. Sensory disturbances (hemisensory deficit)

Lemniscal sensory fibers mostly terminate in the parietal cortex (SI), whereas a significant portion of the ascending spinothalamic fibers terminate in the reticular activating system without reaching the cortex. Superficial sensation impulses are conveyed in the spinothalamic tracts, which synapse in the dorsal horn, cross the midline at spinal level and then ascend through the lateral spinal cord and brainstem. Sensory fibers from the face enter into the ipsilateral descending trigeminal nucleus and cross midline in the upper cervical spinal cord. They then ascend through the medulla, close to the medial lemniscus, and separate to join the medial part of the spinothalamic tract in the pons. The deep sensation fibers ascending in the ipsilateral posterior columns synapse in the gracile and cuneate nuclei of the brainstem. These fibers decussate in the caudal medulla, and then ascend through the brainstem in the medial lemniscus. Fibers carrying deep sensation from the face enter the trigeminal nucleus in the pons and then cross to form the trigeminal lemniscus, adjacent to the medial lemniscus. All ascending sensory fibers through the midbrain project to the thalamic nuclei. Fibers from the thalamic nuclei project to the primary somatic cortex, insula, and the upper part of the Sylvian fissure. The primary somatic cortex has sensory representation resembling those of the motor homunculus (Warlow et al., 2001a).

Evaluation of sensory system dysfunction is important in stroke patients to localize the lesion, to understand functional neuroanatomy, and to further manage additional signs and symptoms. Sensory abnormalities after stroke often lead patients to suffer a central post-stroke pain, involuntary movements (Sharp et al., 1994; Hallett, 1995; Ghika and Bogousslavsky, 1997) including alien hand syndrome (Ay et al., 1998), and abnormal motor execution (Ghika et al., 1998) associated with poor rehabilitation outcome (Stern et al., 1971; Reding and Potes, 1988; Chester and McLaren, 1989; Zeman and Yiannikas, 1989).

Primarily, involvement of the thalomocortical sensory radiation due to an ischemic lesion can produce sensory symptoms (Kim, 1991, 1992, 1994, 1999). Subcortical strokes may cause sensory deficits of both modalities (Shintani, 1998), predominantly spinothalamic (Kim, 1992) or lemniscal sensory impairment (Groothuis et al., 1977). Through the thalamocortical pathway, small lesions produce sensory impairment of a cheiro-oral, cheiro-oral-pedal or cheiro-pedal distribution identical to a thalamic nuclei stroke (Derouesné et al., 1984; Omae et al., 1992; Isono et al., 1993; Kim, 1994, 2002; Yasuda et al., 1994).

Strokes involving the cerebral cortex typically produce an impairment of discriminative sensations

including loss of position sense, topagnosia, graphesthesia, astereognosis, and an elevation of two-point discrimination threshold despite relatively preserved protopathic sensations (Kim, 2002). Verger (1900) and Déjerine and Mouzon (1914) described this parietal cortical sensory syndrome many years ago and this syndrome is usually accompanied by hemiparesis, hemianopia, aphasia, or hemineglect. The propathic sensory impairment may be related to an involvement of the secondary somatosensory area (SII) or the thalamic-SII sensory connection (Kim, 2002). Horiuchi et al. (1996) reported a patient with a pure spinothalamic sensory deficit with an infarct located at the inner part of the parietal operculum. The cortical hemisensory symptoms are observed not only after strokes occurring in the SI or SII area, but also after frontal or posterior parietal lesions, confirming that the sensory cortex is not necessarily limited to the post-central gyrus (Kim, 2002). Some small cortical lesions of the sensory cortex produce sensory symptoms resembling peripheral or root disease (Youl et al., 1991; Bassetti et al., 1993; Kim 1994). Foix et al. (1927) demonstrated that an infarct affecting the anterior parietal region may produce profound hemisensory loss (pseudothalamic syndrome) with little or no accompanying hemiparesis.

25.3.2.4. Visual field disturbances (hemianopia, quadrantanopia)

MCA territory infarction regularly causes hemianopia accompanying hemiparesis, hemisensory loss, and alterations in behavior, but this sign as an indicator of infarct site and size is not well established. Patients may not be aware of their visual deficit or they may not be able to explain their homonymous visual defects. Stroke patients with visual impairment must be evaluated regarding visual stimuli to the eyes, the transmission of information to the occipital cortex and the interpretation of transmitted information. Lesions of different sites through the visual pathway give typical abnormalities. Homonymous visual field deficits in stroke patients suggest the existence of a retrochiasmal lesion. Involvement of optic radiations after the lateral geniculate nucleus produce hemianopia. Lesions of the inferior optic radiation between the lateral geniculate nucleus and the calcarine cortex, where the fibers swing over the temporal horn of the lateral ventricle and deep into the temporal lobe, result in a homonymous superior quadrantanopia, while lesions of the superior optic radiation in the parietal lobe result in a homonymous inferior quadrantanopia (Warlow et al., 2001a). The MCA supplies the superior optic radiation and in case of its occlusion, inferior quadrantanopia occurs. Sometimes, the MCA extends much more posteriorly and causes a homonymous hemianopia. A parietal infarction deep enough to affect the fibers of the upper half of the visual radiation is presumably responsible for the infrequently described inferior quadrantanopia with MCA territory infarction.

25.3.2.5. Aphasia

Global aphasia is the loss of expression and comprehension ability, associated with destruction of anterior and posterior language areas (Kertesz and Phipps, 1977). In general, nonfluent (expressive) aphasia is likely be due to a lesion of the dominant frontal lobe, although not necessarily confined to Broca's area (Mohr et al., 1978a). More than 95% of right-handed people and even most left-handed people have dominance for speech and language in the left hemisphere. Occlusion of the trunk of the MCA or its upper division produces a global disruption of language function. Broca's aphasia is mostly related to left insular region lesions and fluent (receptive) aphasia is due to a more posterior lesion. However, most patients with stroke have a combination referred to as "mixed aphasia," due to more extensive lesions within the dominant hemisphere. Consequently, there is often an associated hemiparesis and hemianopia. The Sylvian fissure of the hemisphere dominant for speech and language is the region most likely to cause symptoms of dysphasia after focal brain lesion. "Crossed aphasia" is a disturbance of language which occurs from a right hemisphere lesion in a right-hand-dominant patient and is seen in about 4% of such patients (Pedersen et al., 1995; Bakar et al., 1996; Warlow et al., 2001a). Neologistic jargon output occurs in Wernicke's aphasia with the lesions of superior temporal and inferior parietal regions (Kertesz and Benson, 1970). The superior posterior temporal branch of MCA is usually involved. Patients with transcortical aphasia usually have lesions in the watershed area between the MCA and PCA circulation (Kertesz et al., 1982). Isolation syndrome or mixed transcortical aphasia lesions tend to surround the MCA territory, often in watershed areas, isolating the language areas (Goldstein, 1948). In left-sided superficial MCA territory infarcts, the clinical pattern includes different types of aphasia besides sensorimotor deficits (Fisher, 1956; Hier et al., 1983a,b; De Renzi et al., 1986; Blecic et al., 1993; Lhermitte et al., 1980). Left-sided superior or anterior division of MCA infarct may cause Broca's aphasia, mutism, and buccolinguofacial apraxia, and less frequently Wernicke's aphasia (Tognola and Vignolo, 1980; Bogousslavsky et al., 1989). Left-sided inferior division of MCA infarction may produce Wernicke's aphasia

or conduction aphasia (Fisher, 1970; Vignolo et al., 1986; Bogousslavsky et al., 1989; Ross, 1993).

25.3.2.6. Visuospatial dysfunction (neglect)

Many patients with stroke fail to respond to stimulation of, or to report information from, the side contralateral to the cerebral lesion. The defective process underlying neglect is probably the impairment of sensory processing. Two types of neglect are considered by neurologists as intrapersonal (to one's own body) and extrapersonal (topographical, to the surrounding environment). "Visuospatial dysfunction" is a better term than "neglect" to broaden the context of the clinical pattern. Visuospatial dysfunction include visual and sensory neglect, visual and sensory inattention or extinction, constructional dyspraxias, and agnosias. Unfortunately, the nomenclature is complex and confused by the use of different terms for the same phenomena. Visuospatial dysfunction includes the following terms: hemi-inattention, sensory or tactile extinction, visual inattention or extinction, allesthesia, anosognosia, nonbelonging, anosodiaphoria, agraphesthesia, asterognosis, geographical disorientation, and dressing apraxia. Visuospatial dysfunction is almost always more severe in posterior parietal lesions of the nondominant hemisphere, particularly those that extend to visual association areas (Warlow et al., 2001a). The frequency of visuospatial dysfunction among stroke patients varies widely in the published literature due to different assessment methods (Bowen et al., 1999). Visuospatial problems are major causes of disability and handicap, impede functional recovery and have been associated, although not invariably so, with a poor outcome (Denes et al., 1982; Kinsella and Ford 1985; Pedersen et al., 1997). In general, the parietal lesion may be associated with an impaired response to stimuli from the opposite side of space, whether from a visual, auditory, or even somatosensory source (Birch et al., 1967; Joanette and Brouchon, 1984). These deficits are thought to reflect impaired input from sensory to motor regions. However a similar disturbance occurs from frontal lesions, as well as cortical or subcortical lesions (Heilman and Valenstein, 1972; Damasio et al., 1980; Stein and Volpe, 1983).

The majority of lesions leading to neglect are right-sided and mostly include subcortical areas of the thalamic nuclei, the striatum, and the anterior and posterior limbs of the internal capsule. Infarcts of the medial and lateral deep perforators of the MCA and ACA cause neglect in about one-third of patients (Ferro et al., 1987). In right-sided superficial superior MCA territory infarcts, the clinical pattern includes visuospatial besides sensorimotor deficits (Cutting, 1978; Ross, 1981; Ellis and Small, 1994).

25.3.2.7. Middle cerebral artery stroke syndromes

The clinical presentation patterns of MCA territory infarcts depend on the site of the occlusion, and the size and side of the infarcts. While some of the clinical syndromes are almost specific to a particular territory, others are highly nonspecific (Bogousslavsky et al., 1989, Coutts et al., 2004).

25.3.2.7.1. Stroke patterns

Acute stroke patterns seen in patients with MCA stenoocclusive lesion are similar to those with ICA stenoticocclusive lesions except for the ocular syndromes and panhemispheric types. However, the frequency of the patterns is different. The first pattern, territorial infarct, is the most frequent pattern in patients with embolic MCA occlusion (Bogousslavsky et al., 1989; Lyrer et al., 1997; Heinsius et al., 1998; Min et al., 2000; Lee et al., 2004a). These infarcts and associated clinical syndromes are described according to the level of occlusion such as the MCA stem, division, and cortical branches. Subcortical infarcts (pattern 2) are subdivided into large striatocapsular infarcts and small basal infarcts (Adams et al., 1983). The latter can manifest as classical lacunar syndromes. Lesions of the LSAs and medullary arteries are involved in this pattern. Athero-occlusive mechanisms are more common than embolism for this group (Lyrer et al., 1997; Min et al., 2000; Bang et al., 2002; Lee et al., 2004a). The combination of these two patterns (territorial and subcortical) is also frequent. Multiple small infarcts in the cortical and subcortical territories are another pattern usually associated with embolic mechanism. The last pattern is the borderzone infarct, which is less frequent in MCA stenosis than ICA atherosclerotic lesions (Lee et al., 2004b). Acute embolic MCA occlusion is not regularly associated with borderzone infarctions (Angeloni et al., 1990; Min et al., 2000).

25.3.2.7.2. MCA stem occlusion

Occlusion of the MCA stem or proximal M1 segment before the LSA origin results in a large infarction in deep and superficial territories. Distal M1 segment occlusion after the LSA origin results only in infarction involving the whole superficial MCA territory (Fig. 25.21). The term malignant MCA syndrome, coined by Hacke et al. (1996), draws attention to the high risk of impending herniation and mortality in these patients.

In patients with MCA stem occlusion, the onset is usually sudden without premonitory signs (Bogousslavsky et al., 1986), but sometimes a stuttering or progressive course can be seen (Caplan et al., 1985). The classical syndrome includes contralateral hemiplegia

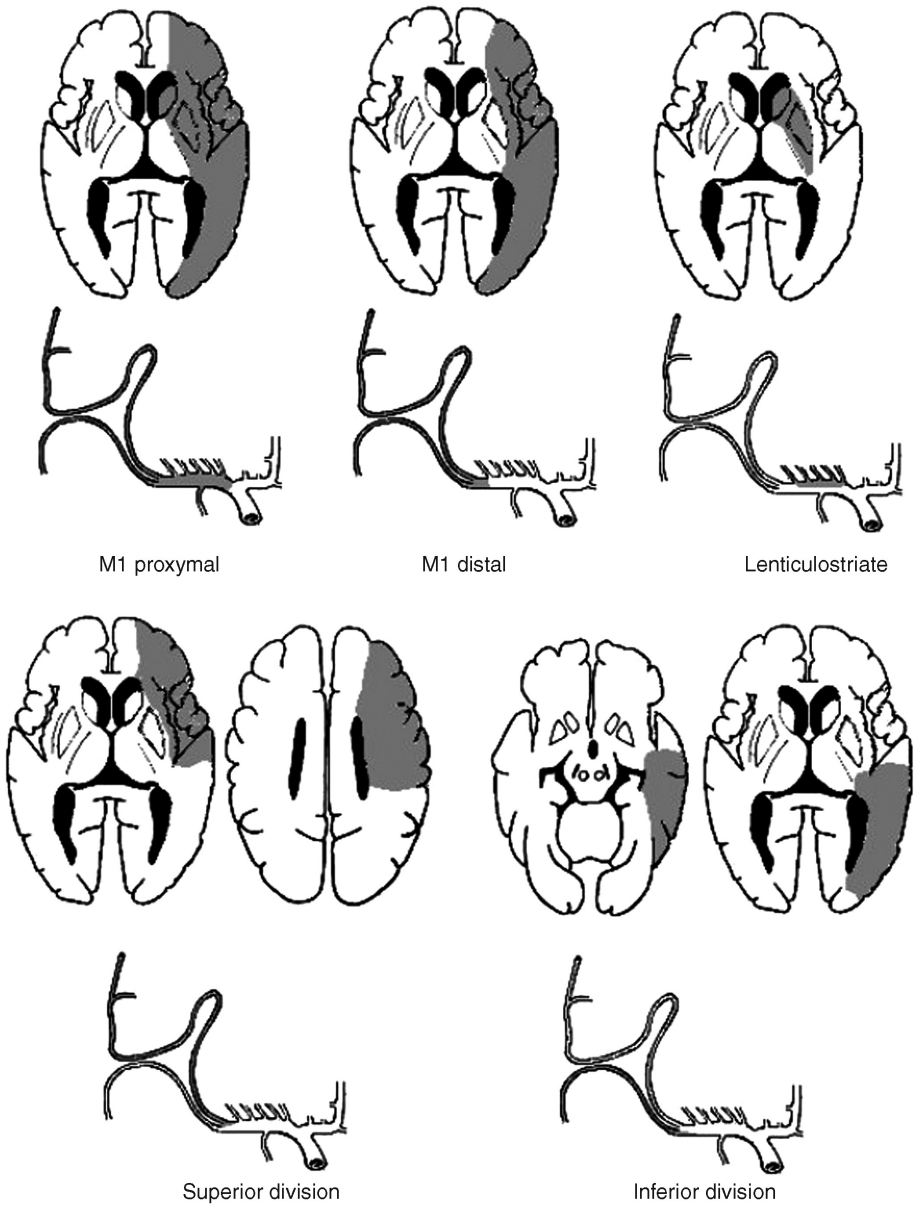

Fig. 25.21. Schematic demonstration of the common infarcted territories and corresponding vascular occlusion sited in patients with proximal MCA strokes (M1 and M2 segments).

or severe hemiparesis with hemihypoesthesia and homonymus hemianopia (Fisher, 1961). Conjugate ocular deviation toward the side of occlusion is usually seen. A global or total aphasia occurs when the dominant hemisphere is affected. In nondominant hemisphere lesions, unawareness of stroke and hemiinattention or neglect of the contralateral side of the space are expected.

During the first few hours after MCA stem occlusion, patients are usually completely awake and alert. Mild drowsiness and confusion can be present. This initial impairment of consciousness is one of the most important short-term prognostic factors (Cucchiara et al., 2004; Georgiadis et al., 2004). In this period, unresponsiveness due to aphasia or neglect should not be misinterpreted as loss of consciousness.

Weakness is usually severe in hemiplegia. The face, arm, and leg are affected with the same severity in MCA stem occlusion. In the occlusion of the distal M1 segment after the origins of the LSAs, hemiplegia sometimes affects the face and arm more heavily than the leg (brachiofacial hemiparesis). Involvement of the insula and operculum results in weakness of the oropharynx in addition to the expected lower facial

plegia. The upper face may fail to wrinkle. Jaw muscles are sometimes obviously weak and impairment of swallowing is seen.

Sensory deficit is characterized by a complete loss of superficial and deep sensations on the whole hemibody (hemianesthesia). A relative preservation of sensory function in the face is commonly seen. In the extremities, sensation is more blunted distally in comparison with proximal locations. Complete astereognosia is almost always seen. Vibration and position sense are heavily affected. Ipsilateral corneal reflex is usually decreased.

Hemianopia is usually accompanied by fixed conjugate with eye and head deviation toward the affected side, known as the Vulpian's sign (Goodwin and Kansu, 1986). Even though the MCA supplies only the upper half of the optic radiation, hemianopia results from involvement of the visual radiation. It is important to note that hemianopia is sometimes difficult to confirm because of the presence of hemineglect for the opposite side of the space and failure to turn toward the side of the hemiplegia in response to sounds from that side. Gaze preferences toward the infarct's side and the absence of blink to thread from that side are more easily elicited. Vulpian's sign usually clears within several weeks (an average of 12 days) (De Renzi et al., 1982). Although this sign is frequently observed in large MCA infarction, it can also be seen with an isolated upper division lesion and more rarely with opercular infarctions.

The global aphasia seen with dominant hemisphere lesions is a type of aphasia that combines the features of both Broca's and Wernicke's aphasias. Patients with global aphasia are unable to speak or follow commands. In some cases, residual speech comprehension may be present. If the nondominant hemisphere is compromised, hemi-inattention or hemi-neglect of the contralateral side of the space ensues. Denial of illness, impersistence, disinterest or poor mentation, apathy, or severe constructional apraxia can be seen (Caplan, 2000).

In patients with MCA stem occlusion, deterioration from massive cerebral edema may occur as early as 36 hours after onset, but is usually more evident by the fourth day (Steiner et al., 2001). A mixed form of herniation develops. Initially, the mass effect results in a shift or displacement of the hemisphere and midline structures to the contralateral side under the falx cerebri. The first herniating structure is the cingulate gyrus. Cingulate herniation may cause ACA compression and related infarction resulting in contralateral leg weakness. Lateral downward transtentorial (uncal) herniation, or central downward transtentorial herniation in more severe cases, also occurs on the ipsilateral side of the midline shift. In central transtentorial herniation, the diencephalons and the bilateral medial temporal lobes are pushed straight down through the tentorial aperture. Clinical signs of the central transtentorial herniation syndrome reflect the nature of rostrocaudal deterioration of the neural structures with progression of herniation. During the earliest stage, defined as the early diencephalic phase, the pupils are small but reactive; cold oculo-vestibular reflex testing may show loss of nystagmus but otherwise no disturbance of eye movements; and the motor response to painful stimulation is purposeful or semipurposeful. During the late diencephalic phase, in addition to these findings, poor or absent reflex vertical gaze, more pronounced drowsiness and usually bilateral corticospinal tract signs are observed. In this phase, painful stimulation usually results in decorticate posturing. With midbrain involvement, the pupils are enlarged and become nonreactive, reflex movement of the eyes is impaired, and painful stimulation elicits a decerebrate posturing. Further progression to the pontomedullary level produces fixed and dilated pupils with total absence of ocular motility and no motor response, or only lower extremity flexion, to painful stimulation. The respiratory pattern worsens from Cheyne–Stokes breathing to central neurogenic hyperventilation, and finally to ataxic and gasping breathing with progression of the herniation. Lateral (uncal) transtentorial herniation occurs when displacement of the medial temporal lobe, especially the parahippocampal gyrus and the uncus, proceeds through the tentorial hiatus. The clinical syndrome again follows a rostrocaudal deterioration pattern. Importantly, there are early signs of third nerve and midbrain compression. The pupil initially dilates as a result of third nerve compression in the diencephalic phase, but later returns to the midposition with midbrain compression.

In central and lateral transtentorial herniation, stretching of the penetrating branches of the basilar artery, which may then rupture, can cause secondary linear hemorrhage, known as "Duret's hemorrhage," in the mesencephalon and pons. This is generally associated with high mortality rates. Hydrocephalus can occur from the obstruction of the aqueduct of Sylvius. Bilateral PCA compression is another complication that can result in bilateral occipital lobe infarcts. In uncal herniation, the contralateral cerebral peduncle becomes compressed against the free edge of the tentorium cerebelli, known as the "Kernohan notch" and results in ipsilateral hemiparesis. Although it is rare, the contralateral pupil can sometimes be affected, even before the ipsilateral one, via a similar mechanism.

If the intracranial pressure (ICP) is monitored, at the time of the first deterioration, it is only moderately

elevated to around 20 mmHg. ICP values subsequently rise over the next 24–48 hours. An ICP higher than 30 mmHg is usually fatal (Schwab et al., 1996). It is important to note that the increase of the edematous infarct volume and tissue shifts develop before, and not always accompanied by, the massive ICP increase. The herniation syndrome without an associated elevation of ICP is also well known (Ropper, 1998). Following significant progression of the herniation, the ICP rises in a rapid and somewhat unpredictable manner.

The prognosis of the patients with large MCA infarcts is poor. Mortality rates vary from 55% to 80% with conventional treatment (Hacke et al., 1996; Krieger et al., 1999; Schwarz et al., 2001). Involvement of the basal ganglia, poor collateral flow, early (during the first several hours) loss of consciousness, progression into coma, pupil abnormalities, the Vulpian's sign, ICP increase, and the need for mechanical ventilation are reported as predictors of early mortality. In survivors, significant disability is a rule. Hemiplegia may improve over a few weeks, with some motor recovery proximally. However, distal limb and facial weakness remain severe. Global aphasia usually improves toward Broca's aphasia with better comprehension, nonfluent agrammatic speech, verbal stereotypies, and poor reading and writing. Nondominant hemisphere signs such as unilateral hemineglect, denial, and impersistence may also improve partly within months.

25.3.2.7.3. Superior or anterior division of MCA territory infarct

MCA superior (anterior) division territory infarction is uncommon (Foix and Lévy, 1927; Mohr et al., 1978b), because the superior trunk is short (20–50 mm) (Foix and Lévy, 1927). The superior trunk supplies a large cortical and subcortical area, including the anterior parietal lobe and most of the convexity of the frontal lobe, with involvement of the precentral and post-central gyri. Superior trunk stroke causes a contralateral hemiparesis with a prominent faciobrachial deficit and hemisensory loss in the same distribution (Neau and Bogousslavsky, 2001). Conjugate eye deviation toward the lesion or a decreased exploration toward the opposite side with the head and eyes remaining in the midline may be observed. A visual field defect may be seen in 2% of patients (Bogousslavsky et al., 1989). In left-sided infarcts, through the course of stroke, Broca's aphasia and buccolinguofacial apraxia may be observed (Tognola and Vignolo, 1980). Wernicke's aphasia may be seen in 2% of patients (Bogousslavsky et al., 1989). Post-stroke depression is also frequently seen after anterior left-sided infarct (Robinson and Starkstein, 1990) and may be associated with nonfluent aphasia (Robinson and Benson, 1981; Signer et al., 1989; Astrom et al., 1993). Patients with right-sided infarcts may have hemi-inattention or hemispatial neglect associated with dysarthria or dysprosodia (Ross, 1981). Acute confusional states may be seen in most patients (Mori and Yamadori, 1987). Denial of the affected side with confabulations may also be seen in these patients (Cutting, 1978; Ellis and Small, 1994).

25.3.2.7.4. Inferior or posterior division of MCA territory infarct

Inferior or posterior division territory infarction represents 14% of the patients of the Lausanne Stroke Registry with damage to the superior and inferior parietal and temporal gyri (Bogousslavsky, 1991b). This neurologic deficit is different from the superior division infarct. The motor weakness is predominantly faciobrachial and mostly mild. The sensory deficit is often associated with extinction contralateral to the lesion on bilateral tactile stimuli (Neau and Bogousslavsky, 2001). Contralateral homonymous hemianopia or upper quadrantanopia is commonly observed (Caplan et al., 1986). In left-sided infarcts Wernicke's aphasia is common (Fisher, 1970; Ross, 1993). In right-sided infarcts, left hemineglect and constructional dyspraxias with behavioral changes may be seen due to involvement of the inferior parietal lobe. Nearly 50% of patients with right-sided infarcts have behavioral changes (Mohr et al., 1978b; Caplan et al., 1986; Mori and Yamadori, 1987). With acute confusional states or acute agitated delirium, patients have vivid hallucinations, delusions, affective and autonomic excitement, agitation, restlessness, insomnia, may be inappropriately unconcerned or jocular, and give continuous moaning-like utterances (Grafman et al., 1986; Mori and Yamadori, 1987). Acute agitated delirium is not observed in MCA superior division territory infarcts and is probably a result of damage to the right middle temporal gyrus and inferior parietal lobule. Sensory aprosody seems to be an acute marker of right inferior division territory MCA infarcts, but may be occasionally seen in right total MCA infarction, right MCA superior division territory infarction (Darby, 1993), and right large subcortical infarction (Wolfe and Ross, 1987). Right posterosuperior temporal lobe damage probably results in sensory aprosody (Darby, 1993).

25.3.2.7.5. Occlusion of the MCA pial branches

Complete MCA pial territory infarct is relatively rare (Bogousslavsky, 1991a,b) without any specific study devoted to this type of infarct (Saver and Biller,

1995). The superior division of the MCA is frequently involved with sparing of the orbitofrontal and anterior temporal branches because these branches originate more proximally or in isolation (Foix and Lévy, 1927). Pial territory infarction is usually due to distal occlusion of the MCA trunk, mainly attributable to embolism (Saito et al., 1987), but may result rarely from in situ atherosclerosis (Ueda et al., 1992; Neau and Bogousslavsky, 2001). Superficial MCA territory infarcts result in faciobrachial sensorimotor deficits and are associated with aphasia or visuospatial impairment depending on the side of the involved hemisphere (Blecic et al., 1993). Faciobrachial hemiparesis, hemiparesis of predominantly leg involvement, or severe hemiplegia can be seen among these patients (Foix and Lévy, 1927; Lascelles and Burrows, 1965; Moody et al., 1990; Mohr et al., 1993). Hemisensory loss, involving tactile and discriminative modalities, usually exhibits the same distribution but often spares the face (Foix and Lévy, 1927). Homonymous hemianopia or upper quadrantanopia, eye and head deviation toward the lesion, are also common (Neau and Bogousslavsky, 2001). Global or Broca's aphasia and ideomotor apraxia in left-sided lesions, and contralateral visuospatial neglect, anosodiaphoria, motor impersistence (Fisher, 1956; Hier et al., 1983a,b; De Renzi et al., 1986), denial of illness (Hier et al., 1983a), inability to maintain eye closure (De Renzi et al., 1986), dressing and constructional apraxia (Hier et al., 1983a,b), acute confusional state (Mori and Yamadori, 1987), or more rarely, sensory aprosodia (Darby, 1993) occur in right-sided lesions (Neau and Bogousslavsky, 2001).

25.3.2.7.5.1. Orbitofrontal artery territory infarct

The orbital portion of the middle and inferior frontal gyri and the inferior orbital part of the frontal lobe are involved (Salamon, 1973; Gloger et al., 1994). The clinical pattern is not verified clearly but patients may have senseless joking, inappropriate playfulness and disinhibition, deterioration of thinking and behavior associated with contralateral forced grasping and conjugate deviation of the eyes (Waddington and Ring, 1968).

25.3.2.7.5.2. Prefrontal artery territory infarct

Occlusion of the prefrontal arteries results in infarction involving the middle frontal gyrus and superior orbital triangular and anterior opercular parts of the frontal lobe (Gloger et al., 1994). The clinical picture is characterized by cognitive and behavioral deficits, a grasp reflex, perseverations with poor abstraction and categorization, impairment of mental flexibility, apathy, and abulia (Mori and Yamadori, 1982; Lhermitte, 1983; Lhermitte et al., 1986; De Renzi and Barbieri, 1992; Saver and Biller, 1995; Neau and Bogousslavsky, 2001). In left-sided lesions, transcortical motor aphasia is common, while right-sided lesions induce motor neglect (Neau and Bogousslavsky, 2001).

25.3.2.7.5.3. Precentral artery territory infarct

The anterior and middle parts of the precentral gyrus, the posterior middle frontal gyrus, and the superior orbital part of the frontal lobe are the territories involved (Neau and Bogousslavsky, 2001). The paresis is usually more prominent in the arm than in the leg (Freund and Hummelshein, 1985). Left precentral artery territory infarct produces a right proximal upper limb weakness with transcortical aphasia and an inability to perform successive motor sequences (premotor syndrome of Luria) (Bogousslavsky et al., 1989). A premotor syndrome is characterized by difficulty in switching one act to another (Freund and Hummelshein, 1985). Patients with motor impersistence cannot sustain simple acts (Lewandowsky, 1907; Fisher, 1956; Kertesz et al., 1985). Hemineglect is seen in retrorolandic lesions (Vallar and Perani, 1986), in right-sided premotor lesions (Castaigne et al., 1972), with difficulties in performing programmed motor acts and delayed reaction times (Heilman et al., 1985; Mohr et al., 1993). Transcortical motor aphasia is the most common aphasia seen in left-sided precentral artery territory infarcts (Alexander et al., 1992). In small studies, several types of aphasia syndromes can be seen among the patients having infarcts in the precentral artery territory as global aphasia, aphemia, pure anarthria, or transcortical sensory aphasia (Van Horn and Hawes, 1982; Schiff et al., 1983; Tranel et al., 1987; Bogousslavsky, 1988; Otsuki et al., 1998).

25.3.2.7.5.4. Central sulcus artery territory infarct

Infarcts of central sulcus arteries include the post-central gyrus and the anterior half of the post-central gyrus. Proximal occlusion of this arterial territory leads to severe hemiparesis, predominantly in face and arm, with hemisensory loss in the same distribution (Waddington and Ring, 1968; Géraud et al., 1970). Distal occlusion of the central sulcus artery produces a clinical picture of motor weakness of the arm with mild hemisensory loss (Neau and Bogousslavsky, 2001). Pure motor hemiparesis involving face, arm, and leg or only the fingers may also be the sole manifestation of central sulcus artery territory infarction (Bogousslavsky et al., 1989; Terao et al., 1993; Lee et al., 1998). In left-sided infarcts, mild Broca's aphasia is typical, whereas in right-sided infarcts, dysarthria may be encountered (Neau and Bogousslavsky, 2001). Dysarthria with mild Broca's aphasia and right faciobrachial weakness is suggestive of central sulcus artery territory infarction, whereas dysarthria with the same motor deficit is found in right-sided infarction

(Bogousslavsky et al., 1989; Neau and Bogousslavsky, 2001).

25.3.2.7.5.5. Anterior parietal artery territory infarct

The posterior post-central gyrus, the parasagittal part of the central sulcus, the anterior part of the inferior parietal gyrus, the supramarginal gyrus and parts of the upper and middle temporal gyri are the areas involved with this type of stroke (Neau and Bogousslavsky, 2001). Anterior parietal artery infarction is very rare (Bogousslavsky, 1992). The most prominent features of infarction of this artery are acute conduction aphasia or acute hemiconcern and a pseudothalamic sensory syndrome or opercular cheiro-oral syndrome (Neau and Bogousslavsky, 2001). The pseudothalamic syndrome includes involvement of elementary modalities of sensation typically affecting the face, arm, leg, and often the trunk, but usually predominating in the upper limb (Foix et al., 1927; Bogousslavsky et al., 1989; Lhermitte et al., 1982; Masson et al., 1991; Bassetti et al., 1993). The infarction always involves the posterior insula, the parietal operculum, the anterior part of the supramarginal gyrus, and the underlying white matter (Pause et al., 1989; Bassetti et al., 1993). The opercular cheiro-oral syndrome is characterized by objective and subjective sensory abnormalities in the face with severe hypoesthesia in the distal limb, involving mainly position sense, stereognosia and graphesthesia and less frequently temperature and pain sensations (Bogousslavsky et al., 1991; Mrabet et al., 1993). In left-sided infarcts, an acute conduction aphasia may be associated with ideomotor apraxia, anomia, acalculia or agraphia (Bogousslavsky et al., 1989; Bassetti et al., 1993). In right-sided infarcts, hemisensory neglect or visuospatial and visuoconstructive abnormalities are common, mainly with involvement of the right inferior parietal lobule (Vallar and Perani, 1986).

25.3.2.7.5.6. Posterior parietal artery territory infarct

The infarction of this territory (the posterior parts of the superior and inferior parietal lobules with the supramarginal gyrus) is unusual and the patients have hemisensory disturbances with impairment of discriminative modalities in one or two parts of the body. It spares touch, vibration, pain, and temperature sensations, and affects graphesthesia, astereognosis, and position sensory loss (Verger, 1900; Déjerine and Mouzon, 1914; Bassetti et al., 1993). The right-sided infarction of this area leads to hemi-extinction and visuospatial and visuoconstructive dysfunction (Bassetti et al., 1993). Left-sided infarction produces Wernicke's aphasia, Gerstmann's syndrome, ideomotor apraxia, anomic aphasia, and phonologic agraphia and alexia (Gerstmann, 1940; Waddington and Ring, 1968; Roeltgen et al., 1983; Rothi et al., 1985; Alexander et al., 1992; Bassetti et al., 1993).

25.3.2.7.5.7. Angular artery territory infarct

Infarction of the angular artery includes the posterior portions of the superior and inferior parietal lobules, the inferior portion of the lateral occipital gyrus, and variable portions of the supramarginal gyrus and angular gyri. Isolated occlusion of this artery is rare. The clinical picture of the distal occlusion produces contralateral hemianopia or lower quadrantanopia (Géraud et al., 1970). In proximal occlusion, the clinical pattern is more severe. A transient motor weakness may be associated with the visual field disturbances and prevalent neuropsychological impairments (Waddington and Ring, 1968; Géraud et al., 1970). Gerstmann's syndrome or angular gyrus syndrome is usually encountered in left-sided lesions (Benton, 1961, 1992). In right-sided lesions, hemispatial neglect with sensory predominance, hemi-extinction on bilateral simultaneous stimulation, asomatognosia, visuoconstructive and visuospatial disturbances, and constructional apraxia are frequent; but Gerstmann's syndrome is exceptional (Moore et al., 1991). Bilateral posterior parietal and angular artery territory infarcts have the clinical pattern of Balint's syndrome (psychic gaze paralysis, visual inattention, and optic ataxia), sometimes with amnesia (Balint, 1909; Rousseaux et al., 1986).

25.3.2.7.5.8. Temporal arteries territory infarct

Specific neurologic features of isolated temporal branch territory infarction have never been clearly defined and infarction of these arteries is usually associated with the posterior parietal artery territory infarction (Neau and Bogousslavsky, 2001). The clinical features of contralateral homonymous hemianopia or superior quadrantanopia, with sometimes slight and transient motor weakness and sensory dysfunction may be found (Foix and Lévy, 1927; Derouesné, 1973; Caplan et al., 1986). Isolated Wernicke's aphasia or Wernicke's aphasia with right hemianopia is an obvious feature and is strongly suggestive of stroke in the left temporal or temporo-occipital artery territory with involvement of the posterior part of the superior temporal gyrus (Bogousslavsky et al., 1989). Left visual neglect, micropsia without spatial neglect, left-sided extinction on bilateral tactile stimuli and constructional apraxia are the most common findings in right-sided lesions (Ceriani et al., 1998; Caplan et al., 1986b). Acute agitated delirium and acute confusional states are observed in left- or right-sided lesions (Caplan et al., 1986; Gustafson et al., 1991).

25.3.2.7.6. Centrum semiovale infarcts

Small or large centrum semiovale infarcts (Figs. 25.17 and 25.21) account for only 1.2–2% of all strokes

(Read et al., 1988; Bogousslavsky and Regli, 1992). The clinical spectrum of medullary perforating artery occlusion is almost the same as the occlusion of deep perforating arteries. Classical lacunar syndromes of pure motor stroke, sensorimotor stroke, and ataxic hemiparesis are the most common clinical pictures (Read et al., 1988; Gutmann and Scherer, 1989; Bogousslavsky and Regli, 1992; Norrving & Staaf, 1991). Small infarcts in this location may often be silent and more frequent than large infarcts (Read et al., 1988). Larger infarcts in this area present with a syndrome similar to more extensive MCA cortical infarction (Bogousslavsky and Regli, 1992). These patients may have weakness/sensory loss predominantly involving the face and arm, aphasia or visuospatial disturbance, or visual field defects according to the tracts affected due to the occlusion. Large infarcts are mostly seen in patients having large vessel disease (Warlow et al., 2001c). The clinical patterns with large infarcts include dysphasia, visuospatial dysfunction, hemineglect, and motor, sensory, or visual field dysfunction. Pure motor stroke is the most frequent pattern, but pure sensory, sensorimotor stroke and ataxic hemiparesis can be observed.

25.3.2.7.7. Striatocapsular infarctions (lenticulostriate infarction)

Lenticulostriate infarcts and striatocapsular infarcts differ in their mechanism process. Lenticulostriate infarcts are a lacunar infarct caused by the occlusion of a single penetrating artery and striatocapsular infarct results from occlusion of multiple lenticulostriate arteries on one side (Pullicino, 2001). Striatocapsular infarcts are usually more than 20 mm in diameter. Although the differences between striatocapsular infarcts and lacunar infarcts have been stressed, the clinical features overlap and striatocapsular infarcts may give rise to the "lacunar" syndromes of pure motor hemiparesis and sensorimotor stroke (Bladin and Berkovic, 1984; Weiller et al., 1990). The lenticulostriate arteries supply the upper part of the anterior limb of the internal capsule, the whole upper part of the internal capsule and corona radiata lateral to the lateral ventricle, the external capsule, the lentiform nucleus, and the body and upper half of the head of the caudate nucleus (Fig. 25.22). The differences in clinical features between striatocapsular infarcts and lacunes are likely to be due to the size of infarct (Pullicino, 2001). Striatocapsular infarcts have a clinical pattern including hemiparesis, hemisensory loss, aphasia, and visual hallucinations (Martin et al., 1992; Weiller, 1995; Pullicino, 2001).

25.4. The anterior choroidal artery stroke syndrome

The anterior choroidal artery (AChA), with an average diameter of 1 mm and length of 25 mm, usually arises from the terminal intracranial ICA just before its bifurcation. It rarely (less than 1% of cases) originates from the MCA or the PComA. The AChA courses along the lateral border of the optic tract, and divides into its branches at the anterior border of the lateral geniculate body. These branches enter the inferior temporal horn and the choroid plexus of the lateral ventricle (Helgason, 1988).

The superficial branches of the AChA supply the optic tract, the optic radiation, the anterolateral half and hilum of the lateral geniculate body and the medial temporal lobe, anterior parts of the hippocampus, and the middle third of the peduncle (Vuadens and Bogousslavsky, 2001; Rhoton, 2002; Hupperts and Lodder, 2004). Perforating branches supply the posterior two-thirds of the posterior limb and the retrolenticular part of the internal capsule, the optic radiation, the medial part of the lentiform nucleus, and the superficial part of the ventrolateral thalamus. Some authors include the posterior paraventricular region in the AChA's territory. Branches of AChA anastomose with those of the PComA, PCA, ICA, MCA and posterior choroidal artery (a PCA branch). Therefore, the AChA territory varies with the number of the anastomoses and the size of their parent arteries (Rhoton, 2002). The anatomical structures consistently located in the AChA territory are the optic tract, the internal capsule

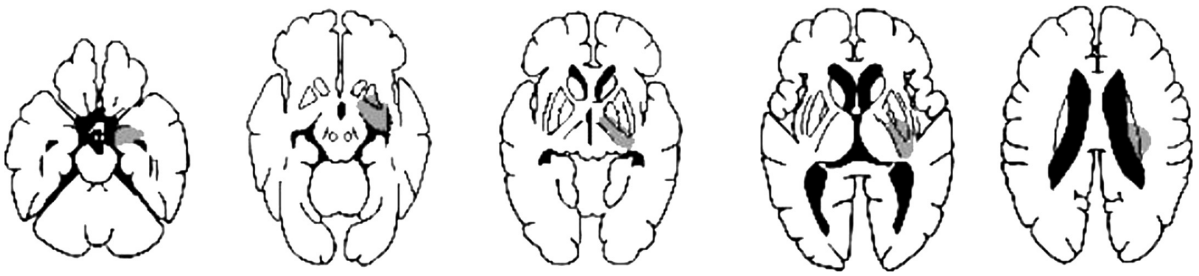

Fig. 25.22. Cartographic representation of the cerebral territory supplied by the anterior choroidal artery. Adapted from Tatu et al. (1998) and Bories et al. (1985).

posterior limb and the choroid plexus (Fig. 25.22) (Mohr et al., 1991; Marinkovic et al., 1999; Rhoton, 2002; Hupperts and Lodder, 2004).

The clinical syndrome of AChA territory infarction depends on the occlusion site. When the main trunk of the AChA is occluded, the infarct size is large. In this less frequent form of AChA stroke, the clinical syndrome it characterizes includes the triad of contralateral hemiparesis, hemianopia, and hemianesthesia. Proprioception is usually spared. Absence of aphasia, problems with consciousness, and head/eye deviation may help for distinction between infarcts from AChA and MCA stem occlusion.

Although contralateral homonymus hemianopia, mainly due to ischemia of the optic tract, is the most common form of visual field defect reported in association with AChA territory infarctions, upper quadrant anopsia, and more specifically upper- and lower-sector anopsia with sparing of the horizontal meridian can be seen. The latter suggests involvement of the corpus geniculatum laterale (Helgason, 1988). In the patients with AChA infarction, hemianopsia can be the sole manifestation (Han et al., 2000). The mesiotemporal lobe and the lateral border of thalamus is usually involved in larger AChA infarcts. Higher cortical signs such as visual neglect, constructive apraxia, anosognosia, and motor impersistence can be seen. Subcortical aphasia is noted in large AChA infarctions in the dominant hemisphere (Vuadens and Bogousslavsky, 2001). Bilateral AChA infarctions, mostly sequential, can present with acute pseudobulbar mutism associated with variable combinations of bilateral hemiparesis, hemiataxia, and hemisensory deficits (Helgason et al., 1988).

Occlusion of penetrating branches of the AChA results in small infarcts (<20 mm in diameter on CT or MRI), and is characterized by classical and atypical lacunar syndromes (see later in this chapter). This kind of presentation is much more frequent than larger infarcts (Hupperts and Lodder, 2004). The most frequent lacunar syndrome is pure motor hemiparesis followed by sensorimotor stroke (Hupperts et al., 1994). Ataxic hemiparesis with hypesthetic ataxic hemiparesis or without hypoesthesia is seen in almost 15% of the patients. Pure sensory stroke is rare but can be observed (Derouesné et al., 1984). In contrast to other small deep infarctions, visual field deficits can be seen, albeit rarely, in small AChA infarctions. In these cases, visual deficits are generally temporary (Hupperts and Lodder, 2004). The prognosis of AChA infarction depends again on the size and mechanism of the stroke. Small, deep, and larger AChA infarctions share the prognostic properties of the lacune and superficial infarcts subtypes (Hupperts and Lodder, 2004).

25.5. Anterior lacunar syndromes

Lacunes are small (volume <15 mm^3), deep infarcts attributable to a primary arteriolopathy of the perforators, frequently caused by hypertension. Most of the lacunar infarcts occur in the territory of the deep penetrating arteries, mainly the lenticulostriate branches of the MCA, but also in the anterior striate and Heubner arteries (branches of ACA), anterior choroidal artery, paramedian branches of the basilar artery, and thalamoperforator branches of the PCA. These territories anatomically correspond to the basal ganglia, lenticular nucleus, and particularly the putamen, thalamus, and white matter of the internal capsule, pons, and centrum semiovale. The lenticulostriates and thalamoperforators have lumen diameters of 100–400 μm, whereas the diameter of the paramedian branches of the basilar artery ranges from 40 to 500 μm. These vessels directly arise from the larger vessels, without the gradual step-down in size that occurs in the distal cortical vessels. They are end-arteries without anastomotic collaterals (Fisher 1965a; Fisher, 1982, Fisher, 1991; Feekes et al., 2005).

Small-vessel atherosclerosis, or microatheroma, usually affect the vessels 200–400 μm in diameter, and are seen in most of the symptomatic cases. Lipohyalinosis, formerly considered the most frequent cause of the lacunes, affects penetrating arteries with a diameter of less than 200 μm in a segmental fashion and accounts mainly for smaller lacunes, which are generally clinically asymptomatic. Among the other causes, microembolism into the penetrating arteries is considered in 4–9% of the lacunes (Fisher, 1991).

Lacunes cause somewhat specific and highly focal symptoms and signs, described in detail below. The five clinical syndromes caused by lacunes ("lacunar syndromes"), either described or revived by C. Miller Fisher in the 1960s and 1970s, are pure motor hemiparesis (Fisher and Curry, 1965), pure sensory stroke (Fisher, 1965), sensorimotor stroke (Mohr et al., 1977), ataxic hemiparesis or homolateral ataxia and crural paresis in the original description (Fisher and Cole, 1965; Fisher, 1978a), and clumsy-hand dysarthria syndrome (Fisher, 1967). In addition to these classical syndromes, several other syndromes have been described, and C.M. Fisher listed more than 70 in his review published in 1991 (Fisher, 1991). However, the five syndromes mentioned are the ones most frequently diagnosed in daily clinical practice and relatively more specific.

It is important to note that the term lacunar syndrome should be restricted to clinical situations in which the likely mechanism of infarction in the territory of a single perforating artery is atherosclerotic arteriolopathy. Reliable ante mortem diagnosis of lacune can only be performed in patients with classical

lacunar syndrome and corresponding acute small deep infarction on a neuroimaging study, preferably diffusion- and perfusion-weighted MRI (Gerraty et al., 2002). It should be realized that any of the classical lacunar syndromes could be caused by atherothrombotic or embolic cerebral large artery occlusion, or even by hemorrhage (Toni et al., 2000; Gerraty et al., 2002).

As a rule, patients with lacunar syndromes should have no clinical signs and symptoms referable to the involvement of the cerebral cortex, such as aphasia, visuospatial neglect, and visual field deficit. The typical brainstem syndromes such as crossed-syndromes with ipsilateral cranial nerve (from third to twelfth, single or multiple) palsy associated with contralateral motor and/or sensory deficit do not suit with the diagnosis of lacunar syndrome as well. Furthermore, unless caused by a coexisting nonvascular condition, no decrease of the level of consciousness is expected in any time during the course of lacunar stroke (Bamford, 2001; Warlow et al., 2001b). Compared with the high prevalence of sudden onset of clinical deficits in patients with acute embolic stroke, the clinical course is often stuttering, stepwise or smoothly progressive over several hours in most (approximately 60%) patients with lacunar stroke (Fisher and Curry, 1965; Marti-Vilalta et al., 2004).

Prior TIAs are documented in almost one-fifth of the patients with lacunar infarcts. Compared with the TIA occurring in larger-vessel strokes, TIAs prior to lacunar stroke tend to be more in number and longer in duration, and the intervals between attacks are shorter (Marti-Vilalta et al., 2004). A particular type of TIA, the so-called "capsular warning syndrome" characterized with pure motor hemiplegia is described. After stereotypical attacks, almost 30% of patients with capsular warning syndrome develop pure motor hemiplegia within 48 hours (Donnan et al., 1993b).

25.5.1. Pure motor hemiparesis

Pure motor hemiparesis (PMH) is the first clinically recognized lacunar syndrome (Marie, 1901; Fisher and Curry, 1965), and is also the most common of the lacunar syndromes, accounting for about one-half to two-thirds of cases (Bamford et al., 1987; Gan et al., 1997; Arboix et al., 2001).

In their classic paper, Fisher and Curry (1965) defined pure motor hemiparesis as "a paralysis complete or incomplete of face, arm and leg on one side, unaccompanied by sensory signs, visual field defect, dysphasia or apractagnosia. In case of brainstem lesions the hemiplegia will be free of vertigo, deafness, tinnitus, diplopia, cerebellar ataxia, and gross nystagmus." The causative lesion can be located in any area where the motor axons within the pyramidal tract are closely packed together. In the original report, causative lacunar infarction was reported to sit in the internal capsule in six and in the basis pontis in the resting three cases (De Freitas et al., 2000). Subsequently, cases with PMH have been reported with lacunes in the corona radiata, the cerebral peduncle, and the medullary pyramid (Chokroverty et al., 1975; Bamford and Warlow, 1988).

Because the clinical picture is identical, differentiating hemiparesis secondary to a capsular lesion (especially the genu and posterior limb) from hemiparesis secondary to a pontine or medullary lesion is impossible (Marti-Vilalta et al., 2004). Patients with left inferior capsular genu infarction may present disorientation memory loss, language impairment, and behavioral changes while patients with right side infarct may show memory impairmental behavioral changes in acute phase of stroke (Bogousslavsky & Regli, 1990b, Martin et al., 1999). However, lacunes in the corona radiata, where the pyramidal motor axons are relatively more dispersed, can cause partial PMH syndromes. These nonproportional syndromes are brachiocrural PMH without face involvement and faciobrachial PMH without leg involvement (De Freitas et al., 2000). Several reports of partial motor syndromes associated with capsular infarcts have been published, suggesting an anteroposterior face–arm–leg somatotopic organization of the corticospinal and corticobulbar tracts in the internal capsule (Manelfe et al., 1981; Tredici et al., 1982). In other patients, however, no reproducible partial hemiparesis pattern was found, confounding the hypothesis of a homunculus organization of fibers in the internal capsule (Donnan et al., 1982; Marti-Vilalta et al., 2004). It is important to note that pure motor monoparesis and isolated facial paresis is more likely to be of cortical origin and almost never seen in lacunes (Fisher, 1982), although some cases, without adequate clinical details or pathologic confirmation, have been defined (Melo et al., 1992b).

In patients with PMH, motor findings were the main clinical presentation, but subtle complaints such as numbness, heaviness can be rarely seen. Of note, dysarthria can also be associated with PMH, but this syndrome, so-called dysarthric hemiparesis, is not a type of lacunar syndrome, and indicates a pontine paramedian infarction in most patients. In general, the clinical course is more benign than that of other types of hemiplegia, particularly larger cortical infarctions. When the hemiparesis is incomplete, the recovery is better (Rascol et al., 1982; Norrving & Staaf et al., 1991).

25.5.2. Pure sensory stroke

Pure sensory stroke (PSS) is the sensory counterpart of PMH. It is far less frequent than PMH, occurring in less than 10% of patients with lacunar infarcts (Bamford et al., 1987; Gan et al., 1997; Arboix et al., 2005).

In his original paper, Fisher defined this lacunar syndrome as "a persistent or transient numbness and mild sensory loss over one side of the body, including face, arm, and leg, without associated hemiparesis, visual field defect, brainstem dysfunction, memory loss, dyslexia, or other deficits" (Fisher, 1965a, 1982). Although the first definition in the original report (Fisher, 1965a) suggested that the sensory loss should be objectively detectable, he noted in a subsequent paper that there could be some cases with persistent sensory symptoms in the absence of objective examination findings (Fisher, 1982).

In the typical complete form of PSS, sensory loss extends over the entire side of the body, involving the face, proximal and distal limbs, and axial structures including the scalp, neck, trunk, genitalia, nose, and tongue. This kind of exact midline split, especially when detected over the trunk, appears to be unique to thalamic and thalamocortical pathway lesions (Fisher, 1965b; Mohr et al., 1978a). Incomplete variants of PSS have also been described. Without pathological confirmation based only on the imaging data, the spectrum of PSS has been extended to the hemisensory symptoms confined to the face, arm, and leg (faciocrural); head, cheeks, lips and head; more restricted forms with unilateral intra/peri-oral and fingers (the cheiro-oral syndrome); face, fingers, and foot (the cheiro-oro-pedal syndrome); shoulder tip and lower jaw; distal forearm alone; fingers alone; and leg alone (Fisher, 1965b; Combarros et al., 1991; Kim, 1992; Arboix et al., 2005).

Patients with complete and incomplete PSS describe their symptoms usually as unpleasant paresthesias and usually feel the parts involved as numb, stretched, hot, or sunburned; and sometimes as heavier, tight, or itching. Contacts with eyeglasses, clothes, and watches transiently make worse the sensory disturbance and may continue after the stimulus is taken away. While all sensory sensations including touch, pinprick, vibration, and position sense, were disturbed in patients with relatively large thalamic infarcts, partial involvement is usually seen in those with smaller infarcts (Kim, 1992). Dysesthesias, or even neuropathic pain, similar to the classic thalamic pain syndrome of Déjerine–Roussy, have also been reported in patients with PSS. The pain may start at the onset of the symptoms or appear hours to months later (Marti-Vilalta et al., 2004).

In the few autopsied cases of patients with PSS, the most common lesion location has been the thalamus, particularly the ventral posterior nucleus (Fisher, 1965b; Fisher, 1978b). The lesions causing PSS are the smallest ones of symptomatic lacunar infarcts. Therefore, CT scan can falsely be negative for lesions in PSS. The clinical course of PSS is usually benign, and the symptoms recede from several days to weeks. However, the symptoms may persist in patients with central post-stroke pain.

25.5.3. Sensorimotor stroke

This lacunar syndrome can be considered as a combination of unilateral PMS and PSS, as the name implies. It was introduced and named by J.P. Mohr and colleagues (Mohr et al., 1977). In this pathologically confirmed index case of sensorimotor stroke (SMS), a lacune in the posteroventral thalamus was found with an additional zone of pallor in the posterior limb of the adjacent internal capsule. Because the vascular supply of the thalamus is separate from the one for the internal capsule, SMS can be considered as an unusual topography for an infarct. However, similar subsequent case reports support that the boundaries between the basal territories of MCA and PCA may not be as strict as previously suggested (Marti-Vilalta et al., 2004). In another pathologically confirmed case of SMA, a lacune located in the internal capsule was found (Tuszynski et al., 1989). After the advent of CT and MR, the lesion spectrum associated with SMS has been expanded. In a series with 12 SMS cases studied with CT, posterolateral aspects of the thalamus were found to be the area most often involved (Allean et al., 1984). In comparison with those with PMH, lesions associated with SMS are more laterally located and larger. In another study, lesion location in SMS was studied with CT in 63 cases, and involvement of the posterior limb of the internal capsule (31%), corona radiata (22%), genu of the internal capsule (7%), anterior limb of the internal capsule (6%), and thalamus (only 9%), was noted (Chamorro et al., 1991).

Even though the frequency in case series of lacunar strokes varies widely, SMS was usually reported to be the most frequent lacunar syndrome after PMS. In a recent well-designed study using clinical and radiological criteria to define the different lacunar syndromes, the prevalence of SMS was found to be 20% (Gan et al., 1997).

25.5.4. Ataxic hemiparesis

This syndrome was introduced and named by Fisher and Cole (1965). It was initially described as homolateral ataxia and crural paresis. The usual clinical features of homolateral ataxia and crural paresis were defined 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" (Fisher and Cole, 1965). In his later paper, Fisher

reported three further cases with prominent vertical nystagmus as well as pyramidal weakness and ataxia. He renamed this syndrome "ataxic hemiparesis," and expanded its spectrum to any combination of ipsilateral weakness and incoordination (Fisher, 1978). As a rule, the severity of ataxia exceeds that attributable to weakness alone. In the usual form, a mild-to-moderate leg weakness, especially the ankle, with little face or upper extremity weakness, is accompanied ipsilaterally by an ataxia of the arm and leg. Sensory variants of ataxic hemiparesis have also been reported.

Lesions producing ataxic hemiparesis disrupt simultaneously pyramidal and frontopontocerebellar tracts. The corona radiata and the anterior limb of the internal capsule are the most common sites (Gutmann & Scherer, 1989). However, in three autopsied cases, Fisher showed contralateral lacunar infarcts located in the basis pontis in all (Fisher, 1978a). It is important to note that these two common lesion locations cannot be discriminated clinically (Marti-Vilalta et al., 2004). In addition to small deep infarcts, larger anterior cerebral artery territorial infarcts have been described as a cause of homolateral ataxia and crural paresis (Bogousslavsky et al., 1992).

Ataxic hemiparesis occurs in as many as 18% of case series of lacunar infarctions (Donnan et al., 1982; Bamford et al., 1987; Gan et al., 1997). Overall prognosis of ataxic hemiparesis is good and improvement occurs within days or weeks. In occasional cases, ataxia persists while the hemiparesis improves (Huang and Lui, 1984).

25.5.5. Dysarthria-clumsy hand syndrome

Dysarthria-clumsy hand syndrome (DCHS) is characterized by the combination of facial weakness, severe dysarthria, and dysphagia, with mild hand weakness and clumsiness (Fisher, 1967; Fisher, 1982). In addition, weakness of the arm or leg may be present (Bamford, 2001). Fisher described DCHS as a variant of ataxic hemiparesis, with the same localizing import. That is, the most frequently involved area is the anterior limb of the internal capsule. However, in Fisher's initial pathologic description, a lacuna was found in the upper paramedian base of the pons (Fisher, 1967). DCHS is rare and its short-term prognosis is favorable (Arboix et al., 2004).

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Chapter 26

Posterior circulation strokes

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Stroke is a leading cause of death and disability in developed countries. As epidemiological projections show, the number of incident strokes will rise by 0.4 million in the EU and European Free Trade Association (EFTA) countries by the year 2050 (Truelsen et al., 2005). Approximately 80% of strokes are of ischemic etiology and 20% are hemorrhagic (Bogousslavsky et al., 1988). Posterior circulation territory is of special interest, as it consists of the posterior pole of the brain, parts of the basal ganglia, cerebellum, brainstem, and spinal cord. Considering the complexity of function directed by posterior circulation structures, clinical symptomatology of posterior circulation strokes might be very complex. Most classic clinical handbooks concentrate on semiology and anatomicopathological correlations of posterior circulation strokes. These masterpieces of clinical medicine are of special value. When approaching an individual patient with stroke, a complex knowledge of anatomoclinical correlations, burden of disease, prognosis for outcome, and risk of stroke recurrence or death, should be of special interest for a management-oriented clinician. In this chapter we will concentrate on the incidence and frequency of posterior circulation strokes as well as on topography, anatomoclinical correlations, cardiovascular risk factors, and etiological subtypes of posterior circulation strokes. We will discuss outcome, stroke recurrence rates and patterns, disability, and case fatality in patients with posterior circulation infarcts and hemorrhages.

26.1. Incidence of posterior circulation strokes

The average annual incidence of transient ischemic attacks (TIA) in the vertebrobasilar distribution was reported to be 20/100,000 population for men, 10/100,000 for women, and 14/100,000 for both sexes (Brown Jr et al., 1998). The incidence of first-ever-in-a-lifetime posterior circulation infarction (POCI) in general population was 34/100,000 (95% confidence interval (CI) = 24–43) and ranged from 8/100,000 (0–20) in subjects aged 25–34 years to 514/100,000 (211–817) in those older than 85 years. In males the total incidence rate was 39/100,000 (24–54), and ranged from 20/100,000 (0–48) in subjects 35–44 years to 318/100,000 (0–759) in those over 85 years of age. In women the total incidence rate was 29/100,000 (16–42) and ranged from 16/100,000 in subjects 25–34 years of age to 596/100,000 (208–984) in those over 85 years of age (Dewey et al., 2003). The annual incidence rate of POCI in an ethnically mixed population was 0.14 per 1,000 population (95% CI = 0.11–0.16). In whites it was 0.14/1,000 (0.11–0.16) and in blacks it was 0.18 (0.09–0.27). The incidence rate ratio adjusted for age and sex for blacks when compared to whites was 1.40 (0.83–2.36). When comparing different social classes the annual incidence rates of POCI were 0.23/1,000 (0.14–0.32) for manual workers, 0.12/1,000 (0.04–0.20) for non-manual workers, and 0.06 (0.004–0.11) for those economically inactive (Wolfe et al., 2002). In the black Caribbean population the crude incidence of POCI was 0.06/1,000 (95% CI = 0.02–0.11) in males and females, and 0.06 (0.03–0.09) for both sexes (Corbin et al., 2004). In the New England Medical Center Posterior Circulation Registry there were 84% whites, 9.5% Asians, 4% blacks, and 2% Hispanics (Caplan et al., 2004e).

An interesting point is the changing of incidence rates of posterior circulation strokes in different time intervals in the same population. One study in a population

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observed for 2 years in a 10-year interval showed that the incidence of all strokes increased due to the increase of the incidence of POCS from 18.2/100,000 (95% CI = 14.9–22.0) in the mid-eighties to 28.3/100,000 (24.4–32.6) in the nineties in both sexes. In men there was an increase from 20.5 (15.6–26.3) to 30.0 (24.4–36.5), and in women the increase of incidence of POCS was as high as 66% from 16.0 (11.7–21.2) in the eighties to 26.6 (21.4–32.7) in the nineties (Johansson et al., 2000b).

26.2. Frequency of posterior circulation strokes

In children aged less than 19 years, ischemic stroke due to an occlusion or stenosis of precerebral portion of vertebral artery constituted only 1% (19/2,278) of all strokes (Fullerton et al., 2003). In young adults 17–45 years of age, vertebrobasilar infarcts constituted 13% of strokes. Three-quarters of them involved vertebrobasilar territory and the rest involved the posterior cerebral artery supply area (Musolino et al., 2003). In patients aged 15–44 years, others reported lower frequency of cerebral infarction in the posterior cerebral artery territory in men (5.1%) than in women (13.5%), with the total frequency of infarcts in this territory equal to 8.6%. On the other hand, infarcts in the supply area of the vertebrobasilar artery were more frequent in men (33.1%) than in women (19.8%), with the total frequency of strokes in this territory as high as 27.6% (Naess et al., 2002c). The percentage of POCI was shown to be higher in patients younger than 85 years (13.9%) when compared to those older than 85 years (11.6%) (Olindo et al., 2003). The frequency of POCI in other community-based studies is shown in Fig. 26.1. In the New England Medical Center Posterior Circulation Registry there were both posterior and anterior circulation strokes. The latter constituted 44% of all strokes (Caplan et al., 2004d). The frequency of vertebrobasilar strokes in different stroke registries and other studies is shown in Fig. 26.2A. An interesting point is the circadian occurrence of stroke. In one report a great preponderance for occurrence of stroke in the posterior circulation during the waking state (92%) when compared to occurrence of stroke during sleep (8%) was demonstrated (Ricci et al., 1992).

26.3. Topography of posterior circulation strokes

The anatomical location of posterior circulation strokes is of special interest for the clinician as it gives both etiological and clinical hints. One of the most widely known registries is the New England Medical Center Posterior Circulation Registry, which is devoted to posterior circulation strokes. In this registry the vertebrobasilar territory is divided into three parts: proximal, middle, and distal territory. The proximal territory is fed by the intracranial vertebral arteries and the posterior inferior cerebellar arteries. This territory contains the medulla oblongata, and the posteroinferior part of the cerebellum. The middle territory is supplied by the basilar artery and its branches, and by anterior inferior cerebellar artery. This territory is composed of the pons and cerebellum. The distal territory is fed by the superior cerebellar arteries, the distal penetrators from the basilar artery, and the posterior cerebral arteries. This territory contains the midbrain and thalamus, as well as the temporal, parietal, and occipital lobe supply zones (Caplan et al., 2004c). The frequency of ischemic strokes in these territories is shown in Fig. 26.2B.

In the Lausanne Stroke Registry (1978–2000) there were 1,244 strokes in the posterior circulation territory (25.9% of all strokes). Topographic location of strokes

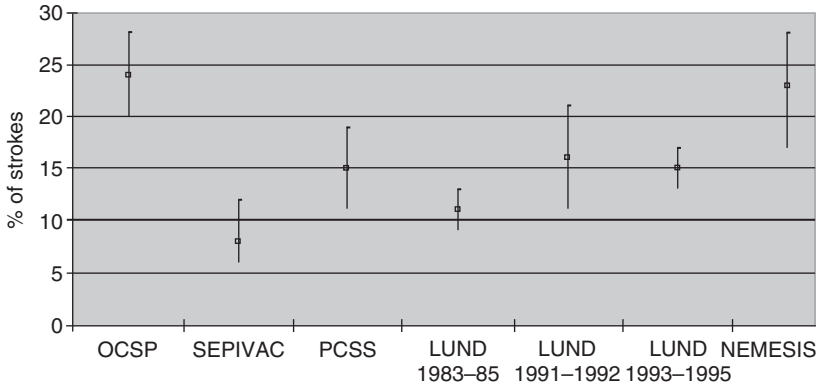

Fig. 26.1. Frequency of POCI (percentage and 95% CI) in community-based studies (first-ever-in-a-lifetime strokes). OCSP: Bamford et al., 1991; SEPIVAC: Ricci et al., 1991a; PCSS: Anderson et al., 1993; LUND: Johansson et al., 2000a; NEMESIS: Dewey et al., 2003.

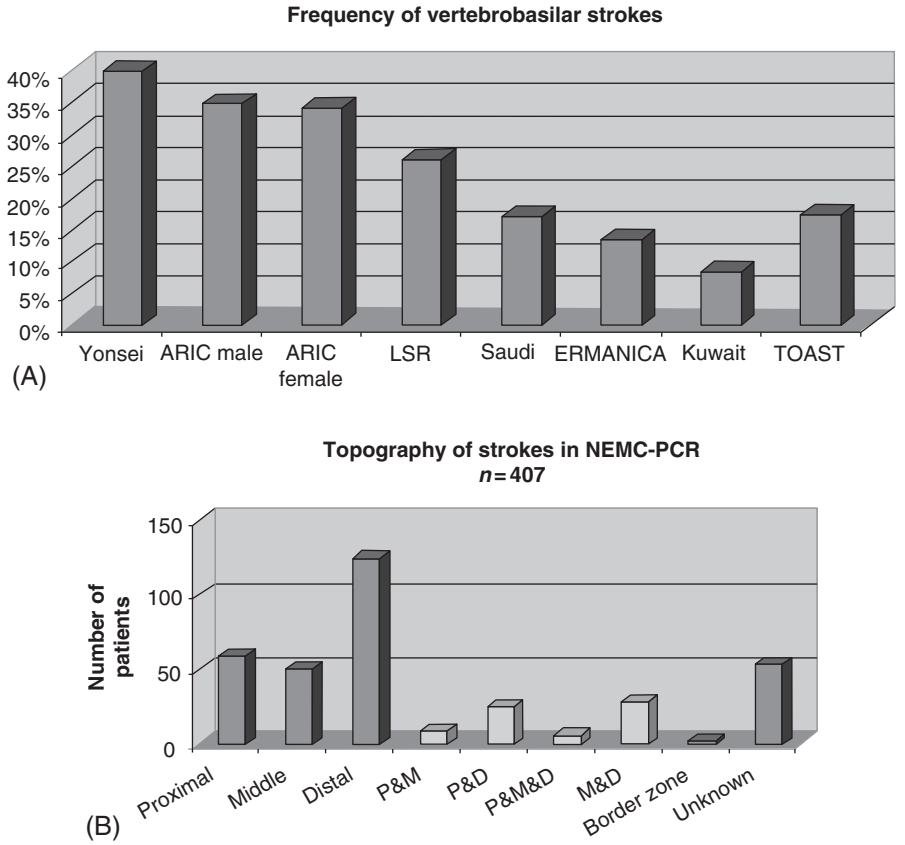

Fig. 26.2. (A) Frequency of vertebrobasilar strokes in stroke registries and in non-epidemiological studies. Yonsei: Lee et al., 2001; ARIC: Toole et al., 1996; Saudi: Yaqub et al., 1991; ERMANICA: Smadja et al., 2001; Kuwait: Abdul-Ghaffar et al., 1997; TOAST: Libman et al., 2001. (B) Frequency of strokes in different posterior circulation territories in the New England Medical Center Posterior Circulation Registry. P&M = proximal and middle territory; P&D = proximal and distal territory; P&M&D = proximal, middle and distal territory; M&D = middle and distal territories.

in the posterior circulation in the Lausanne Stroke Registry is shown in Fig. 26.3.

In the Edge Stroke Registry there were 1,529 strokes registered including 410 (26.8%) in the posterior circulation territory. Of these, 21% of strokes were in the posterior cerebral artery territory (PCA), 7.8% of strokes were within the cerebellum, 48.3% in the brainstem, 9% in the thalamus, and 13.4% in multiple posterior circulation locations (Kumral et al., 1998a).

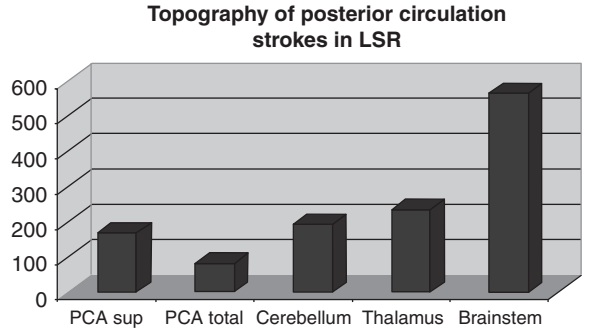

Fig. 26.3. Topographic location of posterior circulation strokes in the Lausanne Stroke Registry. PCA sup = superficial territory of posterior cerebral artery; PCA total = superficial and deep territory of posterior cerebral artery.

In the Athens Stroke Registry, posterior circulation strokes constituted 29.2% (n = 259) of all ischemic strokes. There were 27.4% of strokes in the PCA territory, 23.9% in the cerebellum, 28.2% in the brainstem, 27% in other posterior locations, and 16.2% in multiple posterior locations (Vemmos et al., 2000b).

26.4. Anatomoclinical correlations

The anatomoclinical correlations of posterior circulation strokes have been the subject of multiple reviews and book chapters. In this section we will concentrate on clinical syndromes related to ischemic lesions in different parts of the posterior circulation territory. We will start with syndromes caused by focal ischemic lesions in the posterior circulation territory. In real-life settings it is usually difficult to find pure cases of these syndromes,

and an overlap of these syndromes or an atypical presentation of classic syndromes are most often expected.

26.4.1. Medullary strokes

Historically, the following classic alternating medulla oblongata syndromes are distinguished: Wallenberg, Babinski–Nageotte, Reinhold, Opalski, Hughlings Jackson, Cestan–Chenais, Avellis (palatolaryngeal paresis and contralateral hemiparesis and/or hemihypesthesia), Schmidt, Dejerine, Spiller, and Tapia. The most frequent and clinically relevant syndromes are listed below.

26.4.1.1. Dorsolateral medulla oblongata syndrome (Wallenberg's syndrome)

This syndrome is most often caused by an atherothrombotic occlusion of the vertebral artery. Less frequent causes include small-artery disease and vertebral artery dissection (Kim, 2003). In some cases the posterior inferior cerebellar artery may also be occluded at the orifice. The most common etiological mechanism is thrombotic, and constitutes three-quarters of cases (Fisher et al., 1961b). In young patients with neck pain and Wallenberg's syndrome, vertebral artery dissection may be the most probable cause with or without history of trauma. The anatomical structures that are damaged in Wallenberg's syndrome and respective neurological deficits are listed below (Fig. 26.4).

1. Nucleus of spinal trigeminal tract—ipsilateral decrease of temperature and pain perception;
2. Central sympathetic tract—Horner's syndrome;

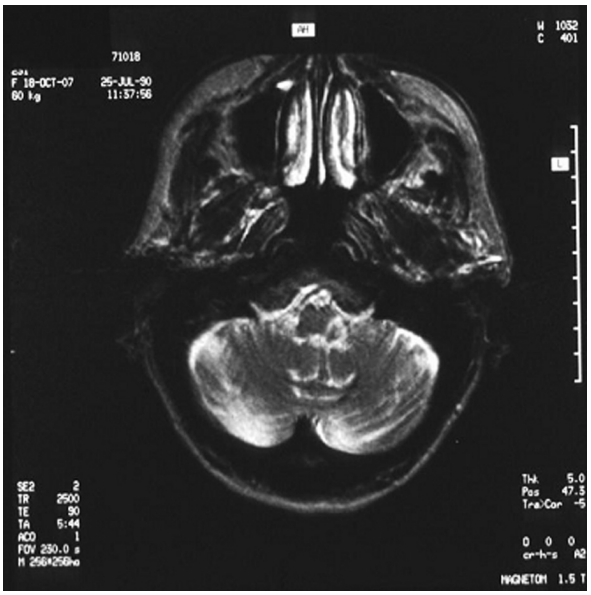

Fig. 26.4. Left lateral medullary infarction (MRI T2-weighted image).

3. Lateral spinothalamic tract—contralateral decrease of temperature and pain perception;
4. Anterior spinocerebellar tract—ipsilateral ataxia and hypotonia;
5. Inferior vestibular nucleus—nystagmus, ipsilateral tendency to fall;
6. Dorsal vagal nucleus—tachycardia;
7. Nucleus of solitary tract—ageusia;
8. Nucleus ambiguous—ipsilateral paresis of soft palate and pharyngeal muscles;
9. Central tegmental tract—myorhythmias of the pharynx;
10. Reticular system—hiccup.

In some patients there may be pain of burning character ipsilateral to the facial sensory loss and involving a small area such as the nasolabial fold, the ear, or the eye (Currier et al., 1961). Variations of the distribution of sensory symptoms in patients with dorsolateral medullary syndrome were reported in the literature. The best known are the Stopford's clinico-topographic correlations (Stopford, 1924). Stopford type I involves cases with far-lateral dorsomedullary strokes and presents with ipsilateral face hypesthesia and contralateral hypesthesia limited to the trunk and lower extremity (so called pseudospinal sensory level) (Bassetti and Bogousslavsky, 1995). In Stopford type II, ischemic lesions are confined to the mediolateral region and present with uncrossed contralateral hypesthesia involving the face, arm and the upper part of the trunk. In Stopford type III, ischemic lesions involve both of the above-mentioned regions (combined far-lateral and mediolateral) and present as a combination of crossed and uncrossed hypesthesia involving ipsilateral face and contralateral hemibody. A new type of sensory disturbance, namely Stopford type IV, was proposed in patients with contralateral hemibody hypesthesia (pure sensory stroke). In these cases lesions were confined to the retro-olivary ventromedial tegmentum sparing the far-lateral medulla and cerebellum (Vaudens and Bogousslavsky, 1998).

Additionally to these symptoms, lateral medullary infarction may also cause various eye-movement disorders (Moncayo and Bogousslavsky, 2003). The most common eye-movement dysfunction in lateral medullary infarction is nystagmus related to damage to the vestibular nuclei or vestibulocerebellar pathways. The following types of nystagmus may be present: torsional, seesaw, horizontal, or horizonto-rotatory (Brazis, 1992). In approximately 70% of cases, skew deviation can be found. Extremely rare is the "floor on ceiling phenomenon," which is an illusionary tilting of the environment by 90–180°. The latter symptoms are linked to the lesions of the otolith pathways in

the vestibular apparatus and brainstem. Of note are also saccadic dysmetria (lesion to the olivocerebellar pathways) and ocular lateropulsion (Tilikete et al., 2001).

26.4.1.2. Medial medulla oblongata syndrome (Dejerine's syndrome)

Medial medullary infarction is rare—less than 100 cases with a detailed clinico-pathological documentation have been published to date. This syndrome is most commonly caused by the occlusion of paramedian branches originating from vertebral and/or basilar artery as well as by the occlusion of the anterior spinal artery. The most common etiology is atherothrombosis (Kim et al., 1995; Bassetti et al., 1997) (Fig. 26.5). Classicaly this syndrome presents with a triad of ipsilateral hypoglossal palsy, contralateral hemiparesis, and lemniscal sensory loss. However, the clinical picture may be heterogeneous. The structures involved and respective neurological symptoms are listed below.

1. Pyramidal tract—contralateral hemiparesis involving face, arm, and leg; spasticity, Babinski sign;
2. Hypoglossal nerve or nucleus of hypoglossal nerve—ipsilateral paralysis of hypoglossal nerve;
3. Olive—myorhythmias of pharynx;
4. Medial lemniscus—contralateral decrease of touch, position and vibration sensibility.

In some cases of paramedian strokes confined to the lower medulla, the pattern of sensory disturbances may involve ipsilateral sensory loss due to involvement of the arcuate fibers. Although extremely rare, in cases with bilateral pyramidal stroke tetraparesis may be present (Nardelli et al., 1978). Although rare, eye movement disturbances such as upbeat nystagmus, lateral gaze palsy, and horizontal nystagmus may also be present in medial medullary infarction, and are related to extension of the ischemic lesion on the adjacent ipsilateral medial longitudinal fasciculus, lower pons, or vestibular nuclei (respectively). Very rarely, bilateral medial medullary infarction may be encountered. Up to now no more than a dozen cases have been reported. Depending on the extent of ischemic lesion tetraparesis, lower cranial nerve dysfunction and consciousness disturbances may be encountered (Katoh and Kawamoto, 2000).

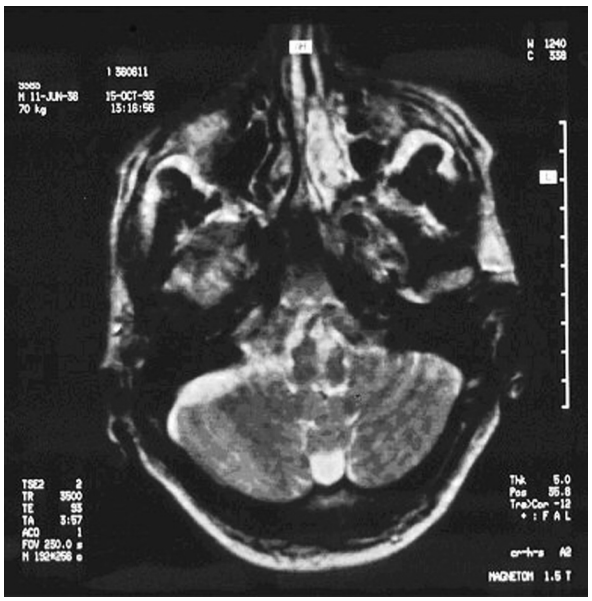

Fig. 26.5. Left medial medullary infarction (MRI T2-weighted image).

26.4.1.3. Lateral and medial medullary infarcts (Babinski–Nageotte's syndrome) and hemimedullary infarcts (Reinhold's syndrome)

Both Babinski–Nageotte's and Reinhold's syndromes are extremely rare. In the majority of cases, Babinski–Nageotte's syndrome is caused by an occlusion of the vertebral artery (Fisher et al., 1961a). Sometimes, vertebral artery dissection may be a causative mechanism of hemimedullary infarction (Irie et al., 2003). The clinical symptomatology contains elements of both lateral medullary and medial medullary syndromes combined. Depending on the level of the infarction an ipsilateral hemiparesis and also a cruciate hemiplegia (an arm on one side and a leg on the other) may also be possible (Vuilleumier et al., 1995) (Fig. 26.6). According to the original descriptions of Babinski–Nageotte's syndrome and the hemimedullary syndrome of Reinhold the clinical feature that allows for the distinction between these syndromes should be hypoglossal palsy.

26.4.1.4. Sub-bulbar infarction (Opalski's syndrome)

A sub-bulbar infarction is extremely rare, and develops due to an occlusion of the posterior vertebrospinal artery. Opalski in 1946 described the syndrome of partial posterior vertebrospinal artery occlusion that includes ipsilateral pain and temperature sensory loss (lesion of the nucleus tractus spinalis of the trigeminal nerve, Opalski's syndrome), Horner's syndrome (lesion of sympathetic fibers descending to the lateral sympathetic nucleus of Jackobsohn), ipsilateral hemiparesis (lesion of the decussated pyramidal tract), ipsilateral ataxia (lesion of the spinocerebellar tract of Fleschig and the tract of Gowers), and contralateral temperature and pain sensory loss (lesion to the spinothalamic tract). Opalski named the sensory symptoms of alternate hypoesthesia for pain and temperature "hemianalgesia alterna subbulbaris" (Opalski, 1946). There are a few

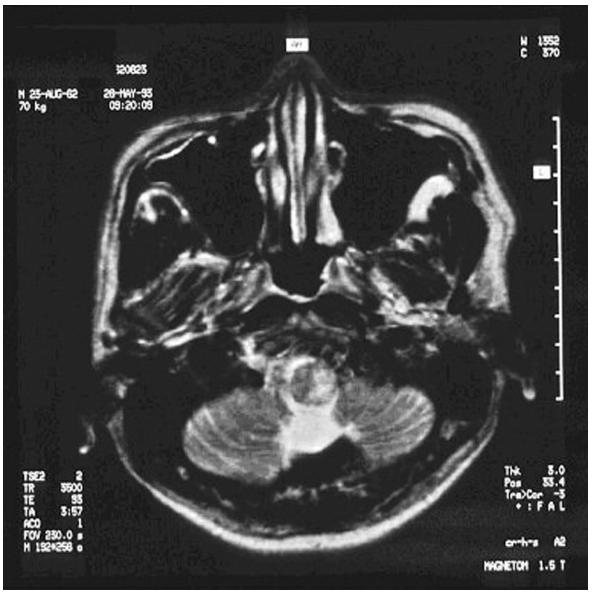

Fig. 26.6. Left hemimedullary infarction (MRI T2-weighted image).

case reports on Opalski's syndrome in the literature stressing a partial presentation of the classic syndrome (Cywiński et al., 1954).

26.4.1.5. Respiratory and autonomic disturbances in medullary strokes

Of great clinical interest, despite their rarity, are the respiratory and autonomic dysfunctions that may be encountered in lateral and medial medullary strokes. There are just a few case reports in the literature of unilateral infarctions involving the pontomedullary reticular formation that caused respiratory dysfunction. In one report a caudal brainstem infarction involving the reticular formation, nucleus tractus solitarius, nucleus ambiguus, and retroambiguus presented with central hypoventilation involving both automatic and voluntary components with a negative response to hypercapnia. Another patient with an infarction in the territory of the medullary reticular formation and nucleus ambiguus had mainly automatic hypoventilation compatible with Ondine's curse (Bogousslavsky et al., 1990). A unilateral medial medullary infarction may also lead to respiratory dysfunction such as irregular (ataxic) breathing as was shown in a case report by Bogousslavsky et al. (1986a). In the medial medullary infarcts a presumed etiology of respiratory dysfunction is the impairment of voluntary respiratory control related to the corticospinal lesion (Bassetti et al., 1997). More recently a combination of life-threatening central hypoventilation and paroxysmal hypertension in a patient with a right lateral medullary infarction was reported (Lassman and Mayer, 2005). Cardiovascular autonomic dysregulation manifesting as impaired heart rate variability was shown to be much more frequent in patients with medullary infarcts than in matched controls (Korpelainen et al., 1996). Although unproven, the role of ischemia of the nucleus tractus solitarius was suggested in various autonomic dysfunctions such as cardiac syndrome X, irritable bowel syndrome, reflex sympathetic dystrophy, late-onset asthma, and essential hypertension (Syme, 2005).

26.4.2. Pontine infarctions

Pontine infarcts constitute approximately 15% of posterior circulation strokes (Bassetti et al., 1996). Multiple alternate syndromes of pontine infarction have been determined thus far including the syndromes of Foville, Millard–Gubler, Raymond, Raymond–Cestan (abducens paralysis and contralateral hemiparesis), Brissaud–Sicard, Gasperini (AICA syndrome and abducens paralysis), Grenet and Gelle ("paralysie alterna de l'acoustique"). The most commonly used ones in contemporary clinical practice are listed below.

26.4.2.1. Ventrocaudal pontine infarction (Millard–Gubler and Foville syndromes)

Ventrocaudal pontine infarction is most commonly caused by the occlusion of circumferential branches of the basilar artery (Fig. 26.7). The anatomical structures involved and corresponding clinical features are listed below.

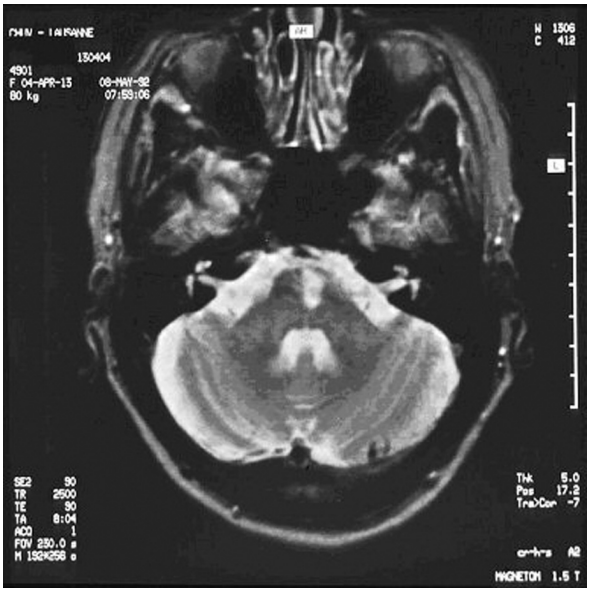

Fig. 26.7. Caudal basal pontine infarction (MRI T2-weighted image).

1. Fibers of the abducens nerve—ipsilateral paralysis of abducens nerve;
2. Pyramidal tract—contralateral hemiparesis;
3. Lateral spinothalamic tract—contralateral decrease of temperature and pain sensation;
4. Nucleus of facial nerve—ipsilateral peripheral paralysis of facial nerve.

Clinical features mentioned above without the eye-movement dysfunction are typical of Millard–Gubler syndrome. Conjugate gaze paralysis added to alternate hemiparesis and facial palsy constitutes Foville syndrome.

26.4.2.2. Midpontine base syndromes

These syndromes are most often due to an occlusion of short circumferential and paramedian perforating branches of the basilar artery (Fig. 26.8). The anatomical structures involved and corresponding clinical features are listed below.

1. Pontine nuclei—ipsilateral ataxia;
2. Corticospinal tract—contralateral hemiparesis;
3. Fibers of trigeminal nerve—ipsilateral paralysis of masticators and decrease of all sensory modalities over the ipsilateral face.

Depending on the location and extension of an ischemic lesion confined to the base of the pons, several clinical syndromes can be distinguished (Schmahmann et al., 2004). In cases with large unilateral basal pontine infarction, *pure motor hemiparesis* involving the face, arm, and leg can be found. The presence of contralateral pyramidal signs of hyper-reflexia and Babinski reflex may indicate the extension of the ischemic lesion to the other half of the basis pontis. *Ataxic hemiparesis* may be found in patients with smaller infarcts in the middle and/or caudal parts of the pons involving the intrapeduncular, peripeduncular, and dorsal as well as ventral pontine regions. Another possible constellation of symptoms is *dysarthria–clumsy hand syndrome*. Topographically, the ischemic lesions may be located in the median, dorsomedial, and paramedian regions; in the medial and intermediate parts of the peri- and intrapeduncular regions; and in ventral and dorsal parts of the pons. *Dysarthria–dysmetria* is a rare presentation of the basal pontine infarction involving the lateral and dorsolateral regions as well as the ventral and lateral parts of the ventral–dorsal regions. *Dysarthria–facial paresis* is also rare and may be related to the ischemic lesions located in the midportions of the basis pontis.

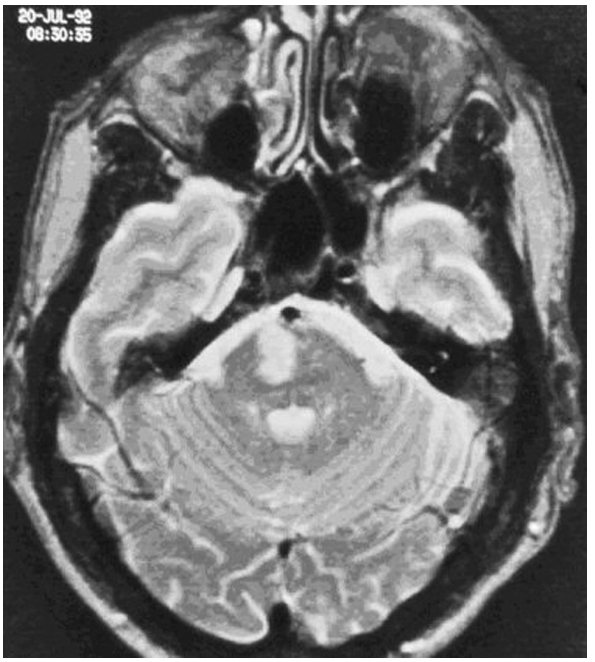

Fig. 26.8. Midpontine basal infarction (MRI T2-weighted image).

26.4.2.3. Tegmental pontine syndromes

26.4.2.3.1. Rostral pontine syndrome

This rare syndrome is most commonly caused by the occlusion of anterior inferior or superior cerebellar arteries (Fig. 26.9). Anatomical and clinical correlations are listed below.

1. Nucleus of spinal tract of the trigeminal nerve—ipsilateral decrease of temperature and pain sensation on the face;
2. Principal sensory nucleus of trigeminal nerve—ipsilateral decrease of touch and discrimination sensation on the face;
3. Motor nucleus of trigeminal nerve—ipsilateral flaccid paralysis of masticators;
4. Tectospinal tract—decrease of blink reflex;
5. Lateral spinothalamic tract—contralateral decrease of temperature and pain sensation;
6. Medial lemniscus—contralateral decrease of touch, position and vibration sensation;
7. Branching corticonuclear fibers—paralysis of facial nerve and lower cranial nerves;
8. Superior cerebellar peduncle—ipsilateral hemiataxia, dysdiadochokinesia.

26.4.2.3.2. Caudal pontine syndrome

This syndrome is usually caused by the occlusion of short circumferential branches of the basilar artery or anterior inferior cerebellar artery. Anatomical structures involved and corresponding neurological findings are listed below.

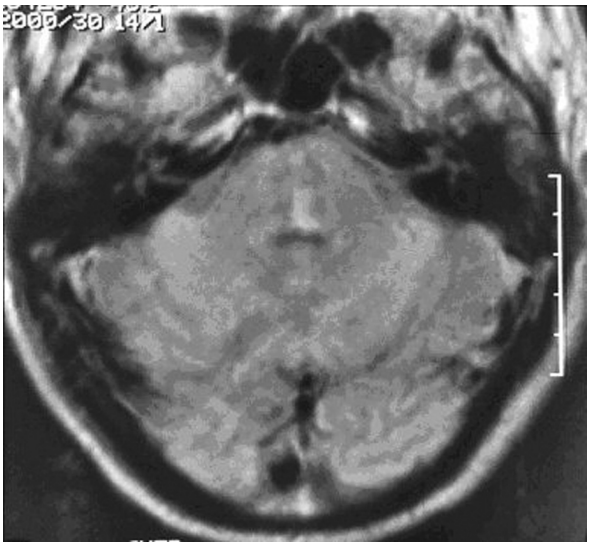

Fig. 26.9. A left pontine tegmental infarction (MRI T2-weighted imaging).

1. Medial longitudinal fasciculus—ipsilateral conjugate gaze paralysis, nystagmus;
2. Nucleus of the abducens nerve—ipsilateral paralysis of eye abduction;
3. Nucleus of facial nerve—ipsilateral peripheral paralysis of facial nerve;
4. Middle cerebellar peduncle—ipsilateral hemiataxia and dysdiadochokinesia;
5. Lateral spinothalamic tract—contralateral decrease of pain and temperature sensation;
6. Medial lemniscus—contralateral decrease of touch, position, and vibration sensation;
7. Central tegmental tract—ipsilateral myorhythmias of soft palate.

26.4.2.4. Eye movement disturbances in pontine infarcts

Eye movement disorders in the pontine region were recently the subject of a thorough review by Moncayo and Bogousslavsky (2003). Eye movement disorders are frequently present as symptoms of pontine infarction. In the *paramedian syndromes* conjugate and disconjugate disorders may be encountered. Among conjugate disorders ipsilateral gaze paresis, complete gaze paralysis, loss of ipsilateral horizontal and/or vertical saccades, downbeating nystagmus, and tonic conjugate deviation of the eyes away from the lesion can be listed. Conjugate disorders are caused by the infarction of the following anatomical structures: abducens nucleus, abducens fasciculus, and paramedian pontine reticular formation (Bronstein et al., 1990; Bassetti et al., 1996; Kataoka et al., 1997). Disconjugate disorders may involve unilateral or bilateral internuclear ophthalmoplegia (WEBINO) syndrome, wall-eyed monocular internuclear ophthalmoplegia (WEMINO syndrome), one-and-a-half syndrome, skew deviation, paralytic pontine exotropia, and ocular bobbing. Lesioned pontine structures include the medial longitudinal fasciculus and the paramedian pontine reticular formation (Kataoka et al., 1997; deSeze et al., 1999).

Lateral pontine syndromes may produce horizontal gaze palsy, nystagmus of horizontal and rotatory characteristics, skew deviation, internuclear ophthalmoplegia, ocular bobbing, one-and-a-half syndrome, and abducens palsy accompanied by a complete AICA syndrome (Gasperini syndrome) (Moncayo and Bogousslavsky, 2003).

26.4.2.5. Multiple pontine infarcts

This syndrome is related to small-artery disease involving perforating arteries supplying the pons. The anatomical structures destructed by the disease process involve corticonuclear fibers. The leading clinical symptoms include spastic paralysis of muscles involved in articulation and swallowing (pseudobulbar palsy).

26.4.2.6. Bilateral pontine infarcts

Acute bilateral infarction of the pons is caused by the atherothrombotic or embolic occlusion of the basilar artery (Fig. 26.10). Clinical findings include abnormalities of the consciousness level, papillary abnormalities, and tetraplegia. In some patients a sentinel mild hemiparesis or some other relatively benign clinical

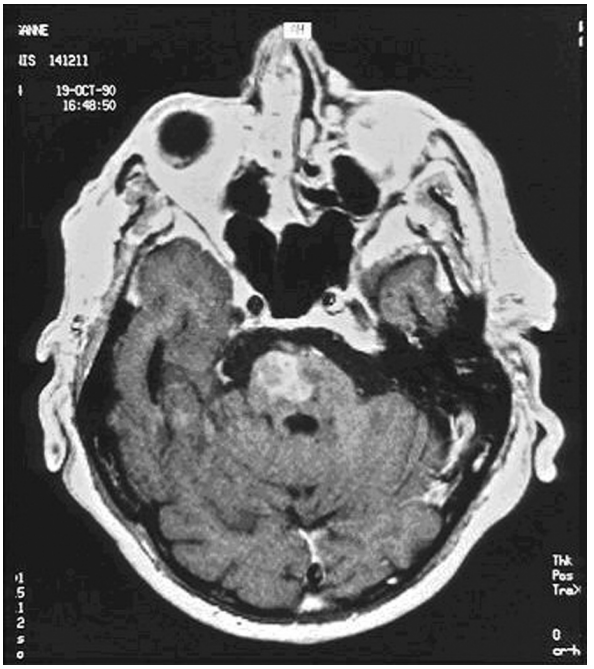

Fig. 26.10. Bilateral pontine infarction (MRI T2-weighted imaging).

symptomatology may precede basilar artery thrombosis. This so-called "herald hemiparesis" that later progresses to tetraplegia and symptoms of bilateral pontine infarction, may represent a progression of thrombosis in the basilar artery (Fisher, 1988).

26.4.3. Midbrain infarcts

The first report on mesencephalic stroke dates back to 1853 (Marotte, 1853). Since then, several clinical syndromes of midbrain stroke have been described including Weber, Nothnagel Claude, Achard–Levi (pupil-sparing oculomotor nerve palsy), and Benedikt syndromes. Isolated midbrain infarcts are rare as the mesencephalic blood supply covers also other posterior circulation territories. Below, the most common mesencephalic syndromes are listed.

26.4.3.1. Lower red nucleus syndrome (Benedikt's syndrome)

In most cases this syndrome is caused by the occlusion of interpeduncular branches of the basilar and/or posterior cerebral arteries (Fig. 26.11). The anatomical structures involved and corresponding clinical features are listed below.

1. Oculomotor nerve fibers—ipsilateral paralysis of oculomotor nerve;
2. Medial lemniscus—contralateral decrease of touch, position and vibration sensation;
3. Substantia nigra—contralateral rigidity;
4. Red nucleus—contralateral chorea, athetosis.

26.4.3.2. Cerebral peduncle syndrome (Weber's syndrome)

Weber's syndrome in most of the cases is caused by the occlusion of the interpeduncular branches of posterior cerebral artery and/or posterior choroidal artery (Fig. 26.12). The anatomical structures involved and corresponding clinical features are listed below.

1. Fibers of oculomotor nerve—ipsilateral oculomotor paresis;
2. Corticospinal and corticonuclear tracts—contralateral hemiparesis with a supranuclear paresis of facial and hypoglossal nerves;
3. Corticopontine tract—contralateral ataxia;
4. Substantia nigra—contralateral rigidity.

26.4.3.3. Claude's syndrome

This rare syndrome was first described by Claude (1912). It is caused by a unilateral infarction in the region of paramedian upper midbrain that involves the third nerve nucleus and/or the oculomotor nerve fibers and cerebellothalamic pathways. Two clinical symptoms are typical for this syndrome: ipsilateral oculomotor nerve palsy and contralateral cerebellar dysfunction (Lefebvre et al., 1993).

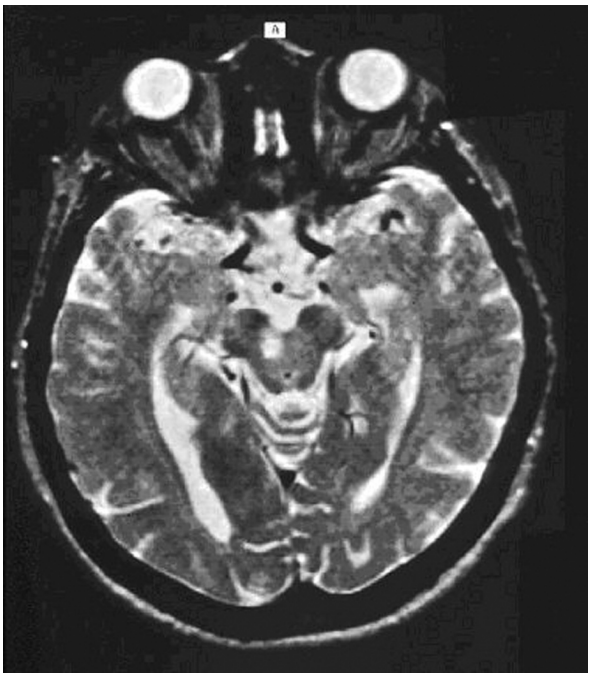

Fig. 26.11. An ischemic lesion in the region of the red nucleus (MRI T2-weighted images).

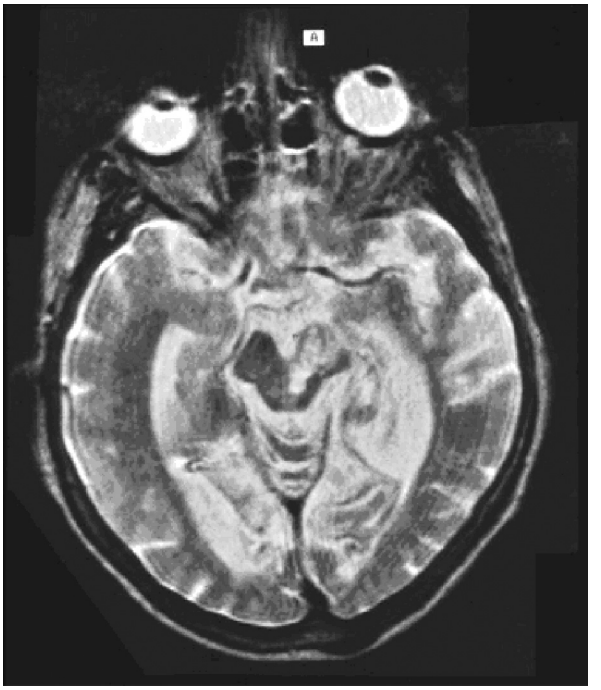

Fig. 26.12. An infarct in the region of the left midbrain peduncle (MRI T2-weighted imaging).

26.4.3.4. Eye movement disturbances in midbrain infarcts

Eye movement disorders in the midbrain region were recently subject of a thorough review by Moncayo and Bogousslavsky (2003). As two of the three nuclei of the nerves innervating extra-ocular muscles as well as vertical gaze centers are located in the midbrain, the eye movement disturbances are often observed in patients with midbrain infarcts. In the *upper midbrain syndromes* the following eye movement disturbances may be encountered (with respective anatomical correlates).

1. Conjugate vertical gaze palsies—isolated up-gaze, down-gaze or combined up- and down-gaze (rostral interstitial nucleus of the medial longitudinal fasciculus, posterior commissure, interstitial nucleus of Cajal);
2. Slowing of smooth pursuit (bilateral medial longitudinal fasciculus);
3. Torsional nystagmus (rostral interstitial nucleus of the medial longitudinal fasciculus, interstitial nucleus of Cajal);
4. Pseudoabducens palsy (descending convergence pathways);
5. Convergence–retraction nystagmus (rostral interstitial nucleus of the medial longitudinal fasciculus, posterior commissure);
6. Disconjugate vertical gaze palsy;
7. Skew deviation;
8. Ocular tilt reaction;
9. See-saw nystagmus.

Middle midbrain syndromes involve nuclear and/or fascicular third nerve palsy. Usually middle paramedian midbrain infarcts produce nuclear oculomotor nerve palsy, and lateral midbrain strokes may cause damage to the third nerve fibers (Bogousslavsky, 1989; Bogousslavsky et al., 1994).

Lower midbrain syndromes are very rare and may present with internuclear ophthalmoplegia (isolated or accompanied by trochlear nerve palsy or dissociated vertical nystagmus) and myokymia of the superior oblique muscle. Unilateral internuclear ophthalmoplegia is related to the involvement of the medial longitudinal fasciculus (Bogousslavsky, 1989).

26.4.4. Cerebellar infarctions

26.4.4.1. Posterior inferior cerebellar artery infarcts

Ischemic strokes in the posterior cerebellar artery (PICA) territory occur most often due to an occlusion of the ostium of PICA that is related to an occlusion of the intracranial part of the corresponding vertebral artery. Most common causes of PICA occlusion are cardiogenic or artery-to-artery embolism (Kase et al., 1993e). An infarct in the PICA territory may involve both brainstem and cerebellar supply areas or one of these separately (Fig. 26.13). In a classic autopsy study medullary involvement in PICA infarcts was found in one-third of cases (Amarenco et al., 1989).

The most common clinical symptoms of cerebellar PICA infarction include a triad of vertigo, headache, and gate imbalance with a tendency to fall to the ipsilateral side (Amarenco, 1991; Kase et al., 1993d). When headaches are unilateral they are usually ipsilateral to the infracted PICA territory. A horizontal nystagmus is also one of the key signs of PICA infarction, and in the majority of cases is ipsilateral (Kase et al., 1993c). The PICA territory infarctions may also present as acute isolated vertigo that resembles labyrinthitis (Amarenco et al., 1994b). In autopsy series, partial PICA territory infarcts constitute as much as 46% of cerebellar infarctions, and infarcts in the territory supplied by the medial branch of PICA (mPICA) constitute 32% (Amarenco et al., 1989).

mPICA territory infarcts involve the dorsal base and ventral apex of the cerebellum as well as lateral and dorsal medulla oblongata in cases. In patients with mPICA infarction, three clinical patterns may be found: pseudolabyrinthine signs with or without concomitant dysmetria, ataxia, and lateropulsion (sparing the medulla), Wallenberg's syndrome (complete or partial), and clinically silent pattern (Amarenco and Hauw, 1990a; Barth et al., 1993).

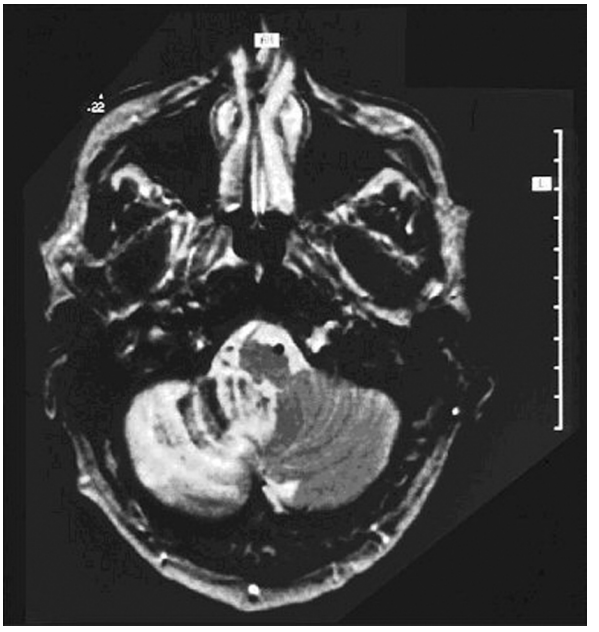

Fig. 26.13. An infarct in the PICA cerebellar supply area (MRI T2-weighted imaging).

Infarcts in the *lateral PICA territory (lPICA)* are rare and involve the anterolateral region of the caudal part of the cerebellar hemisphere. The most common symptoms include unsteadiness, gait ataxia, limb ataxia, dysdiadochokinesia, and ipsilateral body sway. The most common etiology of the lPICA infarcts is vertebral artery atherosclerosis (Barth et al., 1993, 1994). In some cases PICA territory infarcts may present as *acute isolated vertigo*. In these cases vertigo is due to the involvement of vermian uvulonodular complex (Amarenco et al., 1994a).

26.4.4.2. Anterior inferior cerebellar infarcts

Infarctions in the anterior cerebellar artery (AICA) territory are the least common from all cerebellar strokes. The most common cause of strokes in the AICA supply area is occlusion of AICA that coexists with the occlusion of the caudal part of the basilar artery. The most frequent etiological mechanism is atherosclerotic thrombosis. The classic syndrome of AICA infarction includes trigeminal sensory loss, ipsilateral facial palsy, hearing loss, Horner's syndrome, limb dysmetria, and contralateral pain and temperature loss. Complete AICA syndrome was present in 30% of autopsied cases with AICA occlusion. In the same study a devastating presentation of coma and tetraplegia was observed in 20% of autopsied cases (Amarenco and Hauw, 1990b; Barth et al., 1993).

26.4.4.3. Superior cerebellar artery (SCA) territory infarcts

Infarcts in the territory of the SCA are the most common of all cerebellar infarcts, and they rarely involve the total SCA supply area (i.e., cerebellum and brainstem) (Amarenco and Hauw, 1990c) (Fig. 26.14). In the majority of cases these infarcts are caused by cardiogenic embolism (Amarenco and Caplan, 1993). Strokes in SCA territory may also be found in patients with basilar artery occlusion or occlusion of the extracranial or intracranial portion of vertebral artery (Amarenco and Hauw, 1990d). In rarer instances, arterial dissection or fibromuscular dysplasia may be the cause of stroke (Perez-Higueras et al., 1988). The classic SCA syndrome (i.e. that of infarction of the brainstem and cerebellar SCA supply area), is exceptional, and patients present with ipsilateral dysmetria, Horner's syndrome, contralateral abducens nerve palsy, and contralateral pain and temperature sensation loss (Girard et al., 1950; Barth et al., 1993). In the majority of cases, total SCA territory infarctions are accompanied by other vertebrobasilar territory strokes. Occlusion of the SCA may be one of the elements of the top-of-the-basilar-artery syndrome. An infarct confined to a part of the SCA supply territory may also present as cerebellovestibular syndrome with headaches, gait ataxia and vomiting.

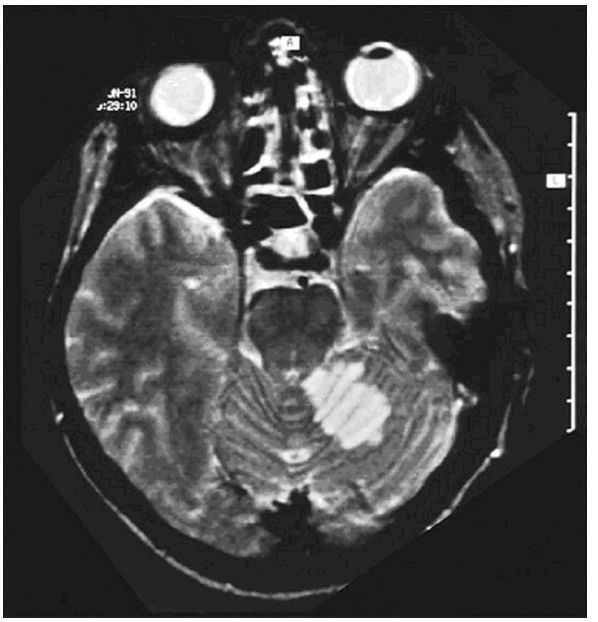

Fig. 26.14. An ischemic stroke in the territory of SCA (MRI T2-weighted imaging).

A characteristic feature of SCA infarction is edema formation and an increased risk of mass effect (Amarenco and Hauw, 1990e; Kase et al., 1993b).

26.4.4.4. Multiple cerebellar infarcts

The most common multiple cerebellar infarcts were shown to occur in the PICA and SCA territories. Other combinations of multiple involvement of different vascular territories were less frequent i.e., PICA & AICA and PICA & SCA (in descending order of frequency). The leading etiology of these infarcts was large-artery disease (Fig. 26.15). The main clinical features included limb and gait ataxia, dysarthria, and motor weakness (Canaple and Bogousslavsky, 1999).

26.4.4.5. Eye movement disturbances in cerebellar infarcts

In patients with cerebellar infarcts, several eye movement disturbances may be encountered (Moncayo and Bogousslavsky, 2003). Although rarely present, in patients with infarction in the SCA territory, multidirectional nystagmus, upbeat nystagmus in primary gaze, and contrapulsion of saccades may be observed (Gilman et al., 1977; Kase et al., 1993a). In cases with PICA territory ischemic strokes, horizontal nystagmus, contralateral rebound nystagmus, and visual tilt illusion may be encountered (Kase et al., 1993f).

26.4.5. Thalamic infarctions

Thalamic infarctions have been the subject of multiple thorough reviews and original publications, the most

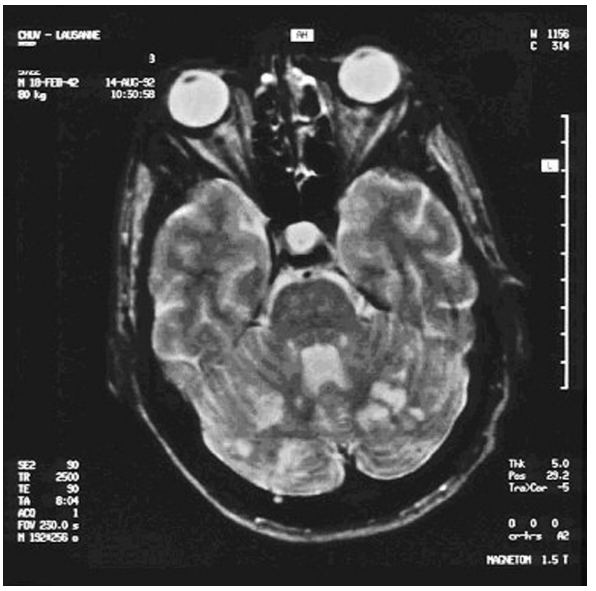

Fig. 26.15. Bihemispheric cerebellar infarcts (MRI T2-weighted imaging).

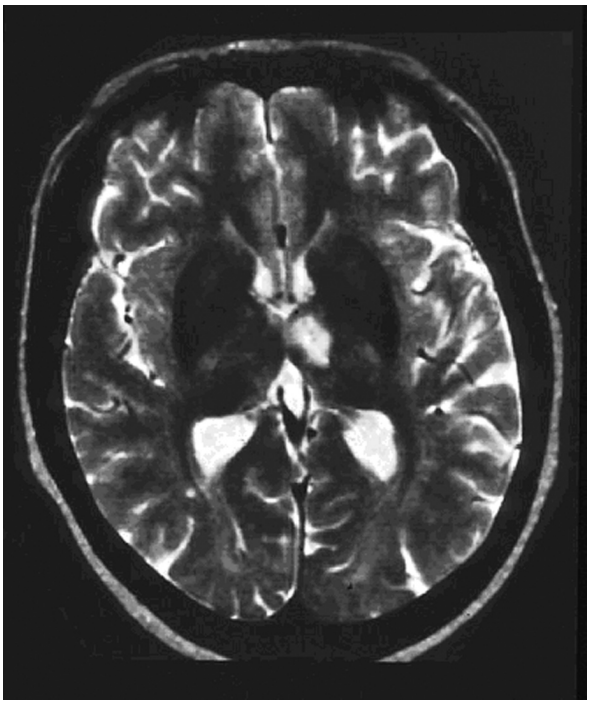

Fig. 26.16. Left tuberothalamic territory infarction (MRI T2-weighted imaging).

recent ones by Schmahmann (2003) and Carrera et al. (2004). Classically, four main arterial thalamic territories are distinguished: tuberothalamic, inferolateral, paramedian, and posterior choroidal, and four major clinical syndromes related to infarcts in these territories are distinguished.

26.4.5.1. Tuberothalamic artery infarction

Tuberothalamic artery is a branch originating from the middle third of the posterior communicating artery. The clinical syndrome comprises mainly neuropsychological features (Bogousslavsky et al., 1986, 1988). The major symptoms include impairment of recent memory, impairment of learning new things, and disorientation in time. In left-sided lesions, language disturbances such as dysarthria, hypophonia, anomia, and decreased verbal and non-verbal fluency may be present. Other functions such as repetition, comprehension, writing, and reading may be preserved (Ghika-Schmid and Bogousslavsky, 2000). In right-sided lesions visual spatial processing may be defective (Fig. 26.16).

26.4.5.2. Inferolateral artery infarction

The inferolateral artery is a branch of the P2 segment of the posterior cerebral artery. An infarct confined to the supply area of the inferolateral artery may lead to a classic syndrome described by Déjerine and Roussy (1906) (Fig. 26.17). Contralateral sensory loss, astereognosis, hemiataxia, spontaneous neurogenic pain, mild transitory hemiparesis, and involuntary choreic and athetotic

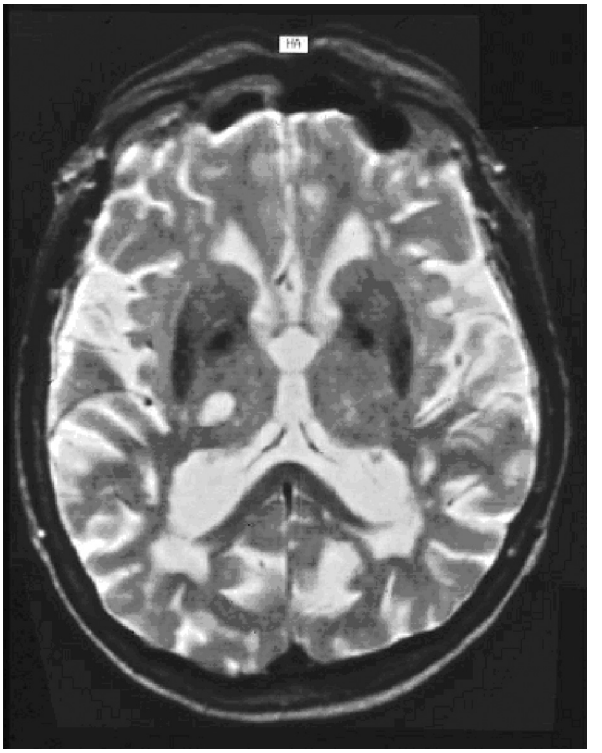

Fig. 26.17. A right inferolateral thalamic infarct (MRI T2-weighted imaging).

movements are the typical features of this syndrome (Déjerine and Roussy, 1906). In later series sensory loss was shown to include all sensory modalities (i.e., touch, temperature, position and vibration sense) but the pattern of sensory abnormalities differed between patients (Bogousslavsky et al., 1988). The occurrence of central pain was linked to infarctions confined to the right thalamus (Nasreddine and Saver, 1997). Another interesting feature of inferolateral artery infarcts is a flexed and pronated hand with an adducted thumb. In the literature this is known as "a thalamic hand" (Foix and Hillemand, 1925).

26.4.5.3. Paramedian artery infarctions

The paramedian artery is a branch of the P1 segment of the posterior cerebral artery (Fig. 26.18). A unilateral infarction in the territory of the paramedian artery produces disturbances of arousal, memory, language, and visual deficits. For the left-sided lesions language deficits (dysprosody of speech, hypophonia, perseverations, reduced verbal fluency) and for the right-sided lesions visual-spatial deficits are characteristic (Guberman and Stuss, 1983). Disturbances of consciousness, emotions, and drive such as confusion, apathy, agitation, and aggression may also be observed (Bogousslavsky et al., 1988). The memory problems caused by an infarction confined to the paramedian artery supply territory resemble those of "thalamic dementia" (Segarra, 1970).

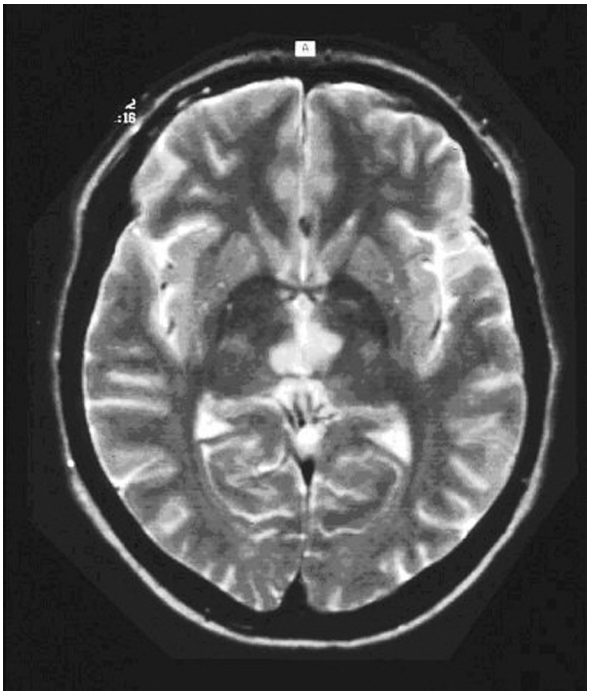

Fig. 26.18. A bilateral paramedian thalamic infarction (MRI T2-weighted imaging).

26.4.5.4. Posterior choroidal infarcts

The posterior choroidal artery is a branch of the P2 segment of the posterior cerebral artery. Ischemic strokes in the posterior choroidal artery territory are quite rare, and have a distinctive clinical symptomatology. The most frequent features are those of visual field disturbances such as quadrantanopsia, and impairment of the fast phase of optokinetic eye movements in a direction contralateral to the ischemic lesion (Bogousslavsky et al., 1988). Homonymous hemianopia, horizontal sectoranopia, eye movement abnormalities, hemisensory loss, and transcortical aphasia memory deficits were described in patients with posterior cerebral artery territory strokes (Neau and Bogousslavsky, 1996). A rare syndrome of a jerky dystonic unsteady hand was described by the same group in patients with an infarct confined to the pulvinar. This syndrome is characterized by ataxia, rubral tremor, dystonia, myoclonus, and choreiform movements (Ghika et al., 1994).

Recently a novel classification system based on variants of distribution of thalamic infarcts was proposed. Approximately 30% of patients with thalamic strokes had thalamic infarcts outside the classic four territories. Therefore three variant distributions were proposed. The anteromedian territory is a combined anterior and paramedian territory. Patients with anteromedially located infarcts should present with cognitive impairment with executive dysfunction, anterograde amnesia, and aphasia (in left-sided or bilateral lesions). The central territory comprises the central part of the thalamus, and infarctions in this area may result in a variety of neuropsychological and neurological signs. Posterolateral territory involves inferolateral and posterior territories. Infarcts confined to this area may produce hemihypesthesia, hemiataxia, executive dysfunction, and in left-sided lesions, aphasia (Carrera et al., 2004).

26.5. Posterior cerebral artery infarcts

The posterior cerebral artery (PCA) territory consists of proximal PCA and superficial PCA supply areas. The proximal or deep PCA supply area consists of the brainstem and thalamic territory. The superficial PCA territory is irrigated by the anterior and posterior temporal, calcarine, and parieto-occipital arteries (Caplan, 1996). In the majority of cases of PCA infarction the etiology is embolic, of either cardiac or arterial origin (Caplan et al., 2004b). Where clinical symptoms are concerned, there is a well-known and interesting mimicry of MCA-like symptoms in PCA territory infarction. In our series there were 18% of patients with PCA infarcts that exhibited typical MCA signs and symptoms that at the same time did not have the classic findings of a PCA stroke.

The most common symptoms of PCA territory infarction mimicking MCA supply area strokes were aphasia (36%), visuospatial neglect (36%), and hemiparesis (19%) (Maulaz et al., 2005).

26.5.1. Deep posterior cerebral artery infarcts

In Lausanne Stroke Registry, deep or proximal PCA infarcts were the most common as they constituted almost 40% of strokes in the PCA supply area. The most prevalent etiology in this territory was lacunar infarction (46%) followed by cardio-embolic stroke (30%). In 60% of patients both motor and sensory deficits were found. Neuropsychological symptoms were detected in 70% of patients, memory problems in 30%, visuospatial neglect in 24%, and aphasia in 16%. The MCA-like symptoms were found in 7.5% of patients with proximal PCA infarctions (Maulaz et al., 2005). The clinical symptomatology of these infarcts is discussed in a more detailed way in the sections devoted to thalamic and midbrain infarcts.

26.5.2. Superficial PCA infarcts

In our material, superficial PCA infarcts accounted for approximately one-third of all PCA territory strokes. The most frequent etiology was shown to be cardio-embolic (54%), followed by unknown (23%), and atherothrombotic (20%) (Cals et al., 2002; Maulaz et al., 2005). The highest frequency of cardio-embolic strokes was similar to other reports (Steinke et al., 1997; Caplan et al., 2004a). Clinical symptoms included visual field defects (89%), motor deficits (36%), and sensory deficits (10%). Neuropsychological deficits were found in approximately 38% of cases (Maulaz et al., 2005). The most prevalent visual field defect was homonymous hemianopia (67%), followed by quadrantopia (22%), and bilateral deficits (7%, including cortical blindness in 4%). Irrespectively of the lesioned hemisphere, the visual cognitive defects included hallucinations (10%) and visual neglect (9%). Agnosia (8.5%) and prosopagnosia (5.5%) were the most frequent findings. When neuropsychological deficits were taken into account the most common was memory impairment (17.5%), dysphasia (14.5%), dyslexia (13%), and disorientation (11%) (Cals et al., 2002). The MCA-like symptoms were present in 33% of patients with superficial PCA strokes, and were the most frequent when compared to other PCA territories infarcts (Maulaz et al., 2005).

26.5.3. Deep and superficial PCA infarcts

Combined deep and superficial PCA ischemic strokes constitute approximately 25% of all PCA infarcts. The most common causes of these infarcts include cardiogenic embolism (34%) and atherothrombosis (20%). However, in the majority of cases (40%) the etiology remains unknown. Among clinical symptoms the most common are visual field defects (82%), motor deficits (76%), and sensory deficits (72%). The most frequent neuropsychological abnormalities include memory problems (54%), followed by visuospatial neglect (44%), and aphasia (28%). The MCA-like symptoms were detected in 12% of patients (Maulaz et al., 2005).

26.6. Particular clinical situations

26.6.1. Basilar artery occlusive disease and multiple infarcts in the posterior circulation

In the large material from the New England Medical Center Posterior Circulation Registry, basilar artery stenosis was found in two-thirds of patients, and basilar artery occlusion in one-third (Voetsch et al., 2004). In Lausanne Stroke Registry, basilar artery stenosis or occlusion was found in 40% of first-ever vertebrobasilar stroke cases, of which 50% were associated with vertebral artery or PCA disease, basilar artery dolichoectasia (Bogousslavsky et al., 1993a). Similar to the data from the literature, in a subgroup of patients with basilar artery occlusive disease we found basilar artery stenosis more frequently than basilar artery occlusion (Devuyst et al., 2002). In the New England Medical Center Posterior Circulation Registry, patients with isolated basilar artery disease, the medial segment of basilar artery was most commonly involved, followed by the proximal and distal segments. The most common combination was proximal and middle segments, and the least frequent was proximal, middle, and distal (Voetsch et al., 2004). In our experience, involvement of the proximal and middle segments of the basilar artery is also the most common (Bogousslavsky et al., 1993a).

Infarcts in the posterior circulation were shown to be most commonly located in the middle posterior territory, followed by the distal and proximal territory. The most frequent single localization is the medial territory, and the most common combined territories location is the middle and distal territory (Voetsch et al., 2004). In Lausanne Stroke Registry, distal posterior circulation territory was the most common single site of infarction, followed by the proximal and medial territory (Bogousslavsky et al., 1993a). In patients with multiple posterior circulation infarcts we found that the most common combinations were proximal and middle/distal territories (Bernasconi et al., 1996).

Recently we coined a term for the specific association of infarction in the posterior inferior cerebellar artery (PICA) and the PCA territory: “proximal–distal

syndrome of the posterior circulation," which is typically due to occlusive disease of the intracranial vertebral arteries, with an in situ bilateral thrombotic occlusion of the origin of PICA accompanied by distal embolism to PCA branches, preserving the whole middle segment of the posterior circulation. Bilateral axial ataxia with visual field defects suggest this pattern of infarction (Piechowski-Jóźwiak and Bogousslavsky, 2004) (Fig. 26.19).

In the New England Medical Center Posterior Circulation Registry the most common primary stroke mechanism was shown to be hemodynamic, followed by cardio-embolism, artery-to-artery embolism, migraine, and other diseases (Voetsch et al., 2004). In our material, large-artery disease was a single cause of posterior circulation infarct in 50% of cases. In the remaining patients, coexisting etiologies such as small-artery disease, basilar artery dolichoectasia, and cardiac embolic sources were present. The other strokes were due to either cardio-embolism, small-artery disease, or undetermined causes, and rarely due to a dissection of the basilar artery or vertebral artery (Bogousslavsky et al., 1993a; Devuyst et al., 2002). The most frequent causes of stroke in our patients with multiple posterior circulation infarcts were, in descending order of frequency, large-artery disease, cardiogenic embolism, and small-artery disease (Bernasconi et al., 1996).

In the New England Medical Center Posterior Circulation Registry cases the clinical course differed between subgroups. In patients with isolated basilar artery disease or generalized posterior circulation involvement, the most prevailing sequence of events consisted of repetitive TIAs followed by stroke, followed by multiple TIAs only, while stroke without TIAs was least frequent. In the group with basilar artery embolism, stroke was usually the first manifestation

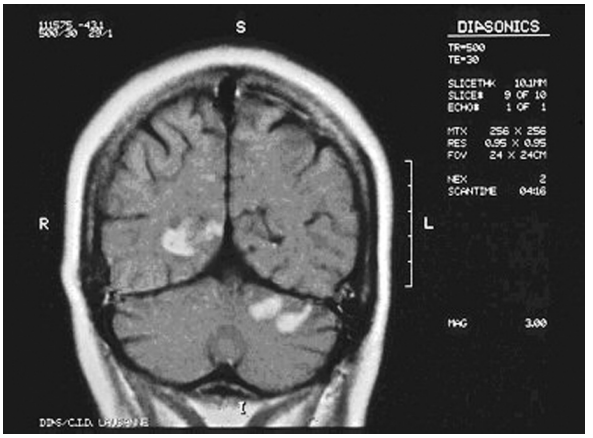

Fig. 26.19. An ischemic stroke confined to the supply areas of the left posterior inferior cerebellar artery and the right posterior cerebral artery.

(Voetsch et al., 2004). In our patients with basilar artery occlusive disease, TIAs preceded stroke in one-third of cases and were also multiple (Devuyst et al., 2002). In patients with multiple proximal and distal infarcts, we found a distinct clinical pattern with non-progressive stroke rarely preceded by TIA (Bernasconi et al., 1996).

In patients with isolated basilar artery disease the most characteristic symptom is hemiparesis; in the group with widespread posterior circulation involvement, vertigo and dizziness; and the group with basilar artery embolism eye movement disorders, decreased level of consciousness and tetraparesis (Devuyst et al., 2002; Voetsch et al., 2004). The most frequent presentation in patients with multifocal posterior circulation infarctions may be the rostral basilar artery syndrome (Bernasconi et al., 1996).

In patients with basilar artery occlusive disease a poor outcome was found in less than one-third of patients. Among the clinical features associated with poor outcome were decreased level of consciousness, tetraparesis, and papillary abnormalities. Basilar occlusion was the pattern associated with the worst outcome, as was the involvement of the distal territory (Voetsch et al., 2004). In our series, death or severe disability was found in half of patients with basilar artery occlusive disease, with clinical predictors including dysarthria, papillary disorders, consciousness disorders, and bulbar symptoms. Cardio-embolism and bilateral cerebellar lesions were associated with poor outcome (Devuyst et al., 2002). In the New England Medical Center Posterior Circulation Registry material the 30-day mortality rate was low and only approximately 20% of patients had major disability (Glass et al., 2002a). Contrary to data from the registry, which showed that one-third of patients with bilateral intracranial vertebral artery disease may die or have severe disability, and that the worst evolution coexisted with occlusion of the intracranial vertebral artery and severe basilar artery occlusive disease (Shin et al., 1999). In our series, the majority of patients with bilateral intracranial vertebral artery occlusion had a better outcome than was previously assumed (Bogousslavsky et al., 1986b). Nevertheless, the embolic etiology was a poor prognostic sign in our patients with multiple posterior circulation infarcts (Bernasconi et al., 1996; Devuyst et al., 2002).

26.7. Risk factors

All classic cardiovascular risk factors can be found in patients with posterior circulation strokes. In a cohort of patients with vertebrobasilar territory infarcts hypertension was present in 55% of cases, diabetes in

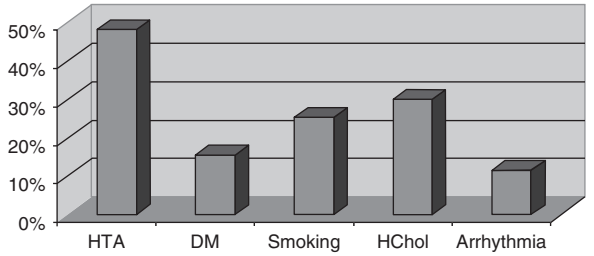

Fig. 26.20. The frequency of cardiovascular risk factors in patients with posterior circulation strokes (n = 1,244). HTA = arterial hypertension; DM = diabetes mellitus; HChol = hypercholesterolemia.

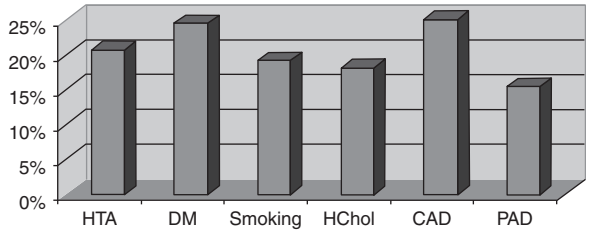

Fig. 26.21. Frequency of major cardiovascular risk factors in patients with posterior circulation strokes in the New England Medical Center Posterior Circulation Registry (n = 407). HTA = hypertension; DM = diabetes mellitus; HChol = hypercholesterolemia; CAD = coronary artery disease; PAD = peripheral artery disease.

35%, heart disease in 50%, smoking in 30%, and hypercholesterolemia in 65% of patients (Abdul-Ghaffar et al., 1997). Lefkovits et al. (1992), in a cohort of 116 patients with vertebrobasilar infarcts, found hypertension in 62% (95% CI = 53–70%) of subjects, diabetes in 11% (7–18), smoking in 41% (33–51), and cardiac disease in 32% (24–55). The frequency of risk factors in the Lausanne Stroke Registry is shown in Fig. 26.20. The frequency of cardiovascular risk factors in the New England Medical Center Posterior Circulation Registry is shown in Fig. 26.21 (Glass et al., 2002d).

26.8. Ischemic stroke subtypes

There are several scales that are used to describe etiological subtypes of ischemic strokes. The most commonly utilized is that used in the Trial of ORG 10172 in acute stroke treatment (TOAST) study, which distinguishes the following categories of stroke: large artery atherosclerosis, cardiac embolism, small-artery occlusion, other determined cause, and undetermined etiology (Adams Jr et al., 1993). In young patients (15–49 years) 60.7% of strokes were shown to be of undetermined etiology, 16.7% were of other determined etiology (10.7% of patients with prothrombotic states, 3.6% of patients with arterial dissection), 10.7% were caused by small-artery disease, 8.3% by large-artery atherosclerosis, and 3.6% by cardiac embolism (Naess et al., 2004). In another study the most common were strokes of other determined etiology and of undetermined etiology and constituted 44.4% of all posterior circulation strokes. The next most common were lacunar strokes (24.4%) followed by cardio-embolic (16.7%) and large-artery strokes (14.4%) (Libman et al., 2001).

When considering etiological subtypes of stroke it is interesting to take a closer look at their topography. A great source of these types of data are stroke registries. In our review we would like to show data from four stroke registries in particular: the Lausanne Stroke Registry (Fig. 26.22), the New England Medical Center Posterior Circulation Registry (Fig. 26.23), the Edge Stroke Registry (Fig. 26.24), and the Athens Stroke Registry (Fig. 26.25).

The Besançon Stroke Registry included 251 patients with posterior circulation strokes. Thirty percent of strokes were of cardio-embolic etiology, 15.5% were due to large-artery stenosis, 19% were caused by large-artery nonstenosing pathology, and 7% were due to small-artery disease (Moulin et al., 1997, 2000). In the Barcelona Stroke Registry there were 635 patients with vertebrobasilar strokes. The authors studied two etiological subgroups of stroke such as nonlacunar (n = 545), and lacunar (n = 90). In the nonlacunar subgroup there were 49% atherothrombotic strokes, 24% hypertensive strokes, 12% cardiogenic strokes, and 15% unknown or unusual etiology strokes. In the lacunar subgroup there were 63% of hypertensive strokes, and 37% of atherothrombotic ones (Marti-Vilalta and Arboix, 1999).

26.9. Outcome and disability

For stroke survivors, their proxies, and care providers the most important issue is the degree of disability and degree of neurological deficit. The scales used most often in clinical settings are the following: for measuring disability, the Barthel Index and Glasgow Outcome Scale; and for assessing the degree of neurological deficit, the modified Rankin Scale (mRS). In young males with posterior circulation infarcts, 21.9% recovered completely and had no neurological deficit on discharge, 71.9% had minor deficit, and 6.3% had severe deficit. Similarly, 20% of young females with POCI had no deficit on discharge, 73.3% had minor, and 6.7% had moderate deficit. When assessing this group of young stroke victims with modified Rankin Scale, on discharge from hospital

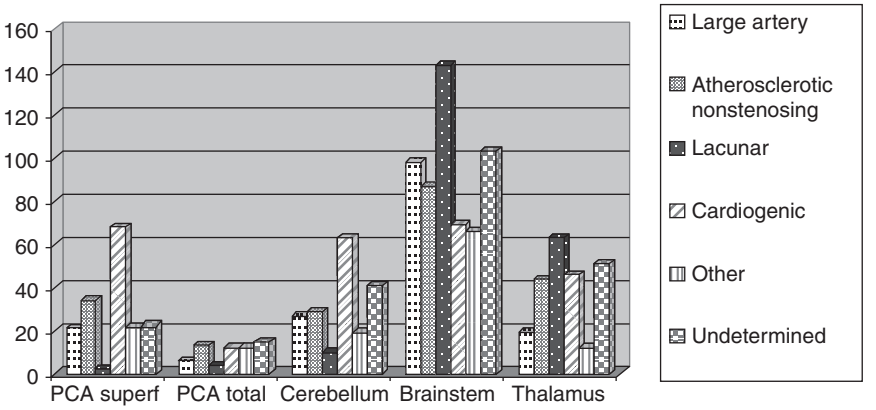

Fig. 26.22. Number of patients with different etiological subtypes of ischemic stroke in posterior circulation territory in Lausanne Stroke Registry (n = 1,244).

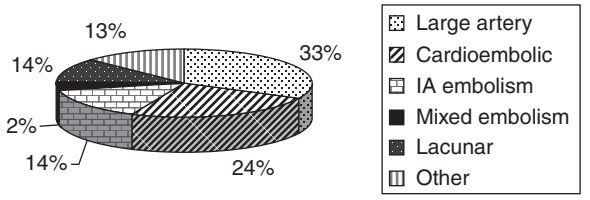

Fig. 26.23. Stroke subtypes in New England Medical Center Posterior Circulation Registry (n = 407).

there were 17.3% of men, and 12.5% of women with mRS = 0. The presence of neurological deficit without disability (mRS = 1) was found in 23.1% of men and 31.3% of women; mRS = 2 was present in 50% of young men, and in 50% of young women. Modified Rankin Scale scores equal to 3 were present in 9.6% of males, and mRS = 4 was found in 3.1% of females (Naess et al., 2002b). In the North East Melbourne Stroke Incidence Study, disability was assessed using the Barthel Index at 3 months and 12 months after index stroke. In patients with POCI, 20% were disabled at 3 months, and 22% at 12 months (Dewey et al., 2003). With a combined assessment based on both Glasgow Outcome Scale and Barthel Index scores, Libman et al. in a cohort of 180 patients with posterior circulation strokes found an excellent outcome in 57.2%, a good outcome in 27.2%, and a poor outcome in 10% (Libman et al., 2001). The degree of neurological deficit in patients with posterior circulation strokes on admission and discharge was assessed by Naess et al. (2002a). There were 3.1% of men, and 12.5% of women without neurological deficit on admission. Minor neurological deficit was found in 50% of men and 43.8% of women. Moderate deficit was detected in 34.4% of men and 25% of women. Severe neurological deficit was found in 12.5% of

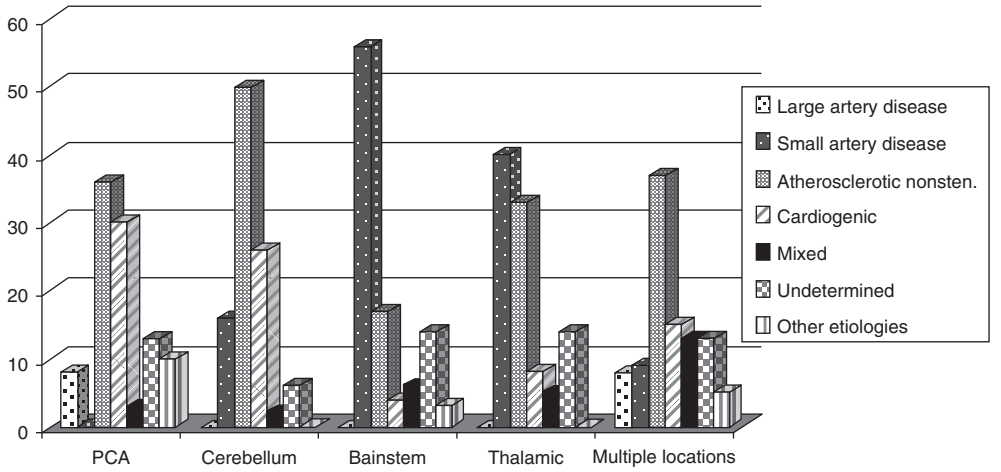

Fig. 26.24. Number of patients with different etiological subtypes of ischemic stroke in posterior circulation territory in the Edge Stroke Registry (Kumral et al., 1998b).

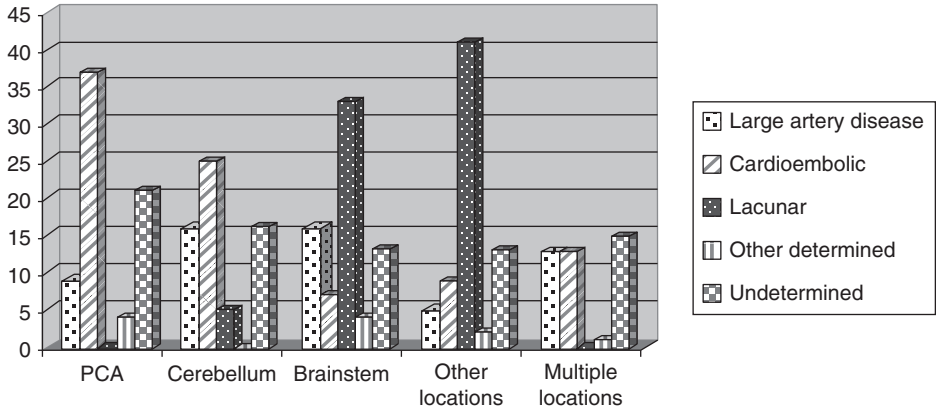

Fig. 26.25. Number of patients with different etiological subtypes of ischemic stroke in posterior circulation territory in the Athens Stroke Registry (Vemmos et al., 2000a).

men and 18.8% of women. On discharge, 21.9% of men and 20% of women had no neurological deficit. Minor deficit was present in 71.9% of men and 73.3% of women. In 6.3% of men and 6.7% of women, moderate neurological deficit on discharge was found (Naess et al., 2002a).

In the New England Medical Center Posterior Circulation Registry, 30 days after disease onset, 28% of patients had no disability, 50.7% had minor disability, and 17.7% had major disability as assessed with the modified Rankin Scale. When taking into account the vascular territory involved, poor outcome was associated with middle (relative risk (RR) = 1.88; 95% CI, 1.28–2.79) and distal (RR = 3.12; 1.92–5.07) location of strokes in the posterior circulation territory. Patients with cardio-embolic strokes were also more likely to have poor outcome (RR = 1.89; 1.28–2.80). The involvement of the basilar artery was also shown to be related to poor outcome (RR = 3.64; 1.90–6.97) (Glass et al., 2002c).

In addition to the Glasgow Outcome Scale, Barthel Index and the modified Rankin Scale, there is another score to assess the health-related quality of life, namely the Assessment of Quality of Life Scale in which 0.0 represents death and 1.0 full quality of life. In patients with posterior circulation strokes the mean Assessment of Quality of Life score at 2 years after stroke was 0.38 (95% CI = 0.28–0.47) (Sturm et al., 2004).

26.10. Case fatality

The case fatality in posterior circulation strokes is not as high as it may appear. In the Netherlands mental health survey and incidence study (NEMESIS) the 28-day case fatality in patients with POCI was 9% (95% CI = 0–18%), at 3 months 16%, and at 12 months 24% (Dewey et al., 2003). Ricci et al. (1991b) reported a case fatality rate of 8.3% (1–27%) at 30 days. Libman et al. (2001) demonstrated a case fatality of 5.6% in patients with posterior circulation strokes. In the Lausanne Stroke Registry the overall case fatality in patients with posterior circulation strokes was 5.9% (4% within 3 weeks) (Bogousslavsky et al., 1993b). In the New England Medical Center Posterior Circulation Registry the 30-day case fatality was lower and equaled 3.2% (Glass et al., 2002b).

26.11. Recurrence

The pattern of recurrence of stroke in posterior circulation has barely been studied in the literature and data is scarce. Modrego et al. (2000) reported 26 recurrent strokes in the posterior circulation from 135 recurrent strokes in all brain territories (19.3%). An interesting point in this study is that in 57.7% of patients with first stroke in the posterior circulation had their recurrence in the middle cerebral artery territory, and that 42.3% had recurrence in the posterior territory. In patients with first stroke in the middle cerebral artery territory 11% had recurrence in the posterior circulation. In the Yonsei Stroke Register, 43.9% of recurrent strokes were in the posterior circulation including 10% of them in the supratentorial territory and 32% in the infratentorial regions (Lee et al., 2001). Dewey et al. (2003) found recurrent POCI in 4% of patients (95% CI = 0–12%).

26.12. Hemorrhagic strokes

When discussing posterior circulation strokes, primary intracerebral hemorrhage (PICH) and subarachnoidal hemorrhage in this territory should be mentioned. Anderson et al. reported the frequency of PICH in

the posterior circulation territory in 25% of cases. The frequency in different anatomical locations was the following: 6.7% in the thalamus, 1.6% in the occipital lobe, 10% in the cerebellum, and 6.7% in the brainstem (Anderson et al., 1994a). In an Indonesian cohort there were 2.6% of PICH in the brainstem and cerebellum (Misbach and Ali, 2001). In a Korean study, the frequency of PICH in the thalamus was 20.9%, in the brainstem it was 7.8%, and in the cerebellum it was 7.4%. The location of ruptured aneurysm in subarachnoidal hemorrhage was 1.7% in the posterior cerebral artery and 20.1% in the posterior communicating artery (Korean Neurological Association, 1993). Others reported the presence of PICH in the vertebrobasilar territory in 6.6% (Eriksson and Olsson, 2001). In the Barcelona Stroke Registry there were 683 cerebral hemorrhages: 13.9% of them were in the posterior circulation territory, 3.8% in the thalamus, 4.7% in the brainstem, and 5.4% in the cerebellum. Among thalamic strokes, 73% were of hypertensive origin, 4% were related to anticoagulation, 4% were due to an aneurysm or arteriovenous malformation, and 19% were of unknown origin. Seventy-eight percent of brainstem hemorrhages were due to hypertension, 6% were caused by an aneurysm or arteriovenous malformation, and 16% were of unknown origin. Hemorrhagic strokes in the cerebellum were mainly caused by hypertension (70%), and unknown or rare causes (24%). In 5% they were due to an aneurysm or arteriovenous malformation (Marti-Vilalta and Arboix, 1999). In the Lausanne Stroke Registry there were 92 first-ever hemorrhagic strokes in the posterior circulation territory. All details concerning anatomical location, presumed etiology, and risk factors are presented in Figs. 26.26 and 26.27. The outcome was also assessed in patients with primary intracerebral hemorrhage. When considering the site of PICH,

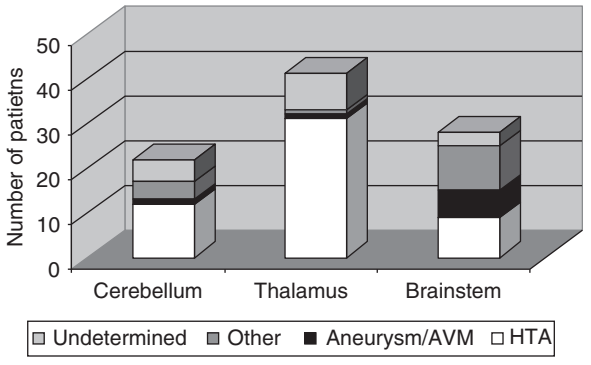

Fig. 26.26. Topography and presumed etiology of posterior circulation hemorrhages in the Lausanne Stroke Registry (n = 92). HTA = hypertension; AVM = arteriovenous malformation.

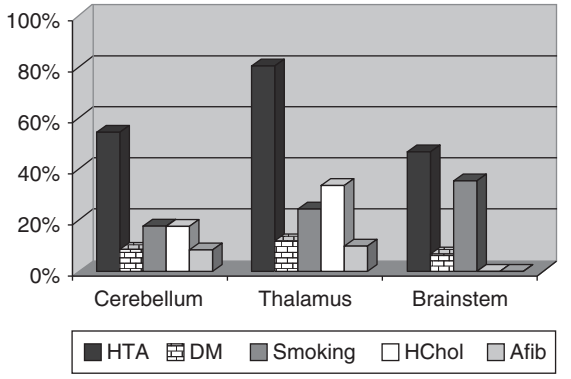

Fig. 26.27. The frequency of risk factors in different topographical locations of posterior circulation hemorrhages (n = 92). HTA = hypertension; DM = diabetes mellitus; HChol = hypercholesterolemia; Afib = atrial fibrillation.

100% of patients with PICH within the brainstem and 30% of patients with cerebellar PICH died within 28 days (Anderson et al., 1994b).

26.13. Summary

The incidence of posterior circulation strokes in the general population ranges from 14 to 34/100,000 population, seems to be higher in men than in women, higher in blacks than in whites, and rises with increasing age. Moreover, the incidence of posterior circulation is rising in time, which reflects the general trend for all strokes. The frequency of posterior circulation strokes is lower than that of anterior circulation strokes and ranges from 8% to 40%. Ischemic strokes in the posterior circulation supply area tend to involve most often the brainstem, the posterior artery territory, and multilevel arterial territories. Arterial hypertension and diabetes mellitus are the most common cardiovascular risk factors in patients with posterior circulation strokes. The leading causes of stroke are large-artery disease, small-artery disease, and cardiogenic embolism. Outcome and prognosis in posterior circulation strokes seem to be much more optimistic than commonly believed, and case fatality is lower than expected. Poor prognosis of patients with embolic strokes deserves special attention. The most frequent site of hemorrhage within the posterior circulation is the thalamus and the most common risk factor is arterial hypertension. Case fatality in hemorrhagic strokes in the posterior circulation is higher than in cerebral infarcts in the same territory. Posterior circulation still remains a secret garden of contemporary neurology despite great progress in diagnostics and treatment. As clinical practitioners expect more attention to strokes in the posterior circulation in acute treatment and stroke prevention trials.

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Chapter 27

Lacunes and lacunar syndromes

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27.1. Introduction

In most cohorts lacunar syndromes comprise about 20% of ischemic strokes. Hence, their importance cannot be underestimated whenever ischemic strokes are considered as a whole. Latterly, this has become even more important as the era of stroke therapy has come upon us. While few would now debate the clinical usefulness of the concept of lacunar infarction and lacunar syndromes, this was not always the case. After being firmly identified as a distinct stroke syndrome by the great French school of neurology early in the twentieth century and the superb clinicopathological studies performed by Fisher 50 years later, controversy raged over the last part of the century as to whether lacunar syndromes were really pathophysiologically different (Marie, 1901; Fisher and Cole, 1965; Fisher and Curry, 1965; Fisher, 1965a, b, 1967, 1968, 1977, 1978a, b, 1979, 1982a, b; Fisher and Caplan, 1971; Fisher and Tapia, 1987; Millikan and Futrell, 1990; Besson, 1991; Besson and Hommel, 1993a, b; Hauw, 1995; Millikan, 1995).

In our view, the robustness of the lacunar syndrome concept has stood the test of time with ample evidence now published to be assured that lacunar infarction is, indeed, pathophysiologically unique and that lacunar syndromes are clinically useful. This is not to say that the story is by any means complete and more data is needed too, particularly in the area of our understanding of the pathogenesis of lacunar infarction itself. There are also a number of areas of uncertainty in the clinical and neuroimaging diagnosis of lacunar infarcts which continue to challenge clinicians. In this chapter we will give a broad overview of lacunar infarction and its clinical expression, lacunar syndromes. Necessarily, this will involve a review of the historical aspects to put our current understanding of such issues as response to therapy in proper context. Much of this has also been presented in a previous publication (Donnan and Yasaka, 1998).

27.2. Historical background

27.2.1. Pathological aspects

Much of the controversy surrounding the term "lacune" in the clinical context is because of its pathological origins. Since much of the early work was published in French language journals, it is useful to read several extra excellent reviews by French investigators published more recently (Besson, 1991; Besson and Hommel, 1993a; Hauw, 1995). In essence, three types of cavity deep within the brain were originally described although there was some overlap in terminology. These are discussed below.

27.2.1.1. Cerebral porosis

In a classic publication in 1901, Pierre Marie described cavities of various sizes around oval smooth margins (Marie, 1901). Reuling and Herring had earlier postulated that these may be generated by the bacillus *Aerogenes capsulatus* and, therefore, a product of post mortem change (Reuling and Herring, 1899). Interestingly, Pierre Marie was in agreement: "In none of the cases that I have studied was there slightest symptom which would suggest a lesion in the nervous system, and yet in one of these cases the peduncles harboured huge cavities" (Marie, 1901). He thought the temperature may have contributed to the genesis of these

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post mortem bacterial changes: "Finally, all the cases I have studied come from autopsies carried out during the hottest months of the year." Hence, the basis of the term "cerebral porosis" was certainly not related to cerebral infarction.

27.2.1.2. "État crible"

This term was used by Durand-Fardel who defined small, multiple lesions, often in the white matter of the insular and having small blood vessels in their center (Durand-Fardel, 1842). A variety of explanations were provided by investigators ranging from the dilatation of blood vessels (Durand-Fardel, 1842), lymphatic sheaths of small arteries (Bizzozero, 1868; Obersteiner, 1872; Ripping, 1874; Arndt, 1875; Pick, 1890), and/or dilatation Virchow-Robin spaces (Adler, 1875; Pick, 1890), or aggregation of lacunes (Proust, 1866). État crible was also described by Pierre Marie although he used the term "perforated state" of the brain. His belief was that "there are some reasons to believe that this perforated stage is due rather to a massive reaction of the cerebral parenchyma than to a local lesion" (Marie, 1901). Further views on état crible were provided by Hughes (Hughes, 1965) as well as Cole and Yates who proposed that this was related to unfolding of penetrated arteries and then enlarged the perivascular space (Cole and Yates, 1967). Hence, the most likely explanation for état crible is perivascular space enlargement although some authors probably confused these lesions with true lacunes. More recently, Poirier developed a new classification for brain cavities (I to III) and his type III cavities would be consistent with the original description of état crible: "dilatation of perivascular spaces. These cavities were rounded, regular, and were centred by a patent vessel with normal walls. The brain tissues appeared more compressed than destroyed" (Poirier et al., 1983).

27.2.1.3. Lacunes

Dechambre in 1838 was the first to use the term "lacune" (Dechambre, 1838). Durand-Fardel as well as Marie in 1901 were also clear that lacunes were quite different to état crible (Dechambre, 1838; Marie, 1901). Marie noted that lacunes were "small and irregular (the size of a bird seed, pea or haricot bean)." Probably because they appeared to be associated with atherosclerosis, he raised the possibility that they could be due to infarcts:

> *One could therefore picture the anatomo-pathological process of formation of lacunes in the following manner; the influence of the general causes of atherosclerosis, the vessels which irrigate the brain change, the nutrition of the brain diminishes, its parts become atrophied, which contributes to the dilatation of the ventricles of the perivascular spaces. As the vascular lesions progress, one or more small vessels break or are obliterated, hence the production of one or more lacunes. In effect, it is known that in the central areas of the brain the blood vessels are terminal, that is, there are no anastomoses, so that the whole territory is irrigated by the blood vessel which is obliterated is inevitably infarcted. (Marie, 1901)*

Interestingly, the footnote was made that "some lacunes may be attributed to a kind of destructive invagination (vaginalite destructive) which would cause a change in the adjacent nervous tissue, as if by a gradual erosion."

There were now two competing theories for the development of lacunes, infarction versus destructive invagination (Catola, 1904; Foix and Nicolesco, 1923; Foix and Chavany, 1926; Moore, 1954). While Ferrand documented the evolution of lacunes from rarefaction through to sclerotic scar, he was not convinced that these were infarcts because the accompanying vessels were not included (Ferrand, 1902). The invagination theory was supported by a number of investigators while Moore had the view that "perivascular encephalolysis" was due to local release of a lytic agent from blood vessels, perhaps due to systemic diseases such as diabetes. Indeed, Hughes may have been the most insightful in that he more clearly established the relationship between small deep infarcts and hypertension (Hughes, 1954).

Hence, although considerable progress had been made, there was still great uncertainty as to the cause of lacunes up to this time. Then, in a series of carefully performed studies from the mid-1960s through to the 1990s, Miller Fisher quite clearly established that lacunes were due to local infarctions in the territory of single penetrating vessels (Fisher and Curry, 1965; Fisher, 1991). He was also responsible for further establishing the role of hypertension in this process by demonstrating associated small-vessel lipohyalinotic damage (see pathogenesis for more details). Others also drew attention to the role of hypertension in the genesis of lacunar infarcts (Prineas and Marshall, 1966; Cole and Yates, 1967).

27.2.2. Clinical aspects

Although often not recognized, Marie gave a remarkably precise description of pure motor hemiplegia in 1901. He noted:

The most frequently observed symptom is hemiplegia ... In most cases there is no loss of consciousness ... characteristically incomplete ... rarely accompanied by deviation of tongue or face or bi-hemianesthesia. I have never observed hemianopia ... permanent aphasia is not found with lacunes; and speech difficulties are extremely common; what is observed is not however an aphasia but a dysarthria, which can be so pronounced that the patient's speech is almost unintelligible. (Marie, 1901)

Fisher then further refined the clinical expression of lacunar infarcts in a series of careful clinicopathological correlations which have become classics of the neurological literature (Fisher and Curry, 1965; Fisher, 1968, 1977, 1978a, b, 1979; Fisher and Caplan, 1971; Fisher and Tapia, 1987).

Transient clinical events preceding lacunar syndromes were also documented as early as 1901 by Marie. He noted that "the multiplicity of episodes, with a variable interval between them, is an essential characteristic of lacunar degeneration. Of my 50 cases, 32 had 2 or more previous episodes." Fisher and Curry (1965) supported this view with the observation: "In our experience a burst of frequent hemiplegic expels suggest the pure motor syndrome arising more likely in the capsule than in the pons." Presenting sometimes as a crescendo of clinical events, this phenomenon has been termed the capsular warning syndrome and is associated with a high risk (about 30%) of lacunar stroke within the next 10 days (Donnan et al., 1993b, 1995, 1996).

27.3. Epidemiology

Based on the very early clinical and pathological studies of lacunar infarction it was extremely difficult to obtain an accurate estimate of the proportion of all strokes which were lacunar. Indeed, prior to the introduction of imaging techniques such as CT and MR, information from reasonably large cohorts was lacking. Fortunately, the introduction of stroke units during the 1970s together with CT coincided with a revival of interest in lacunar syndromes and a number of hospital-based series were published (Mohr et al., 1978; Chambers et al., 1983; Bogousslavsky et al., 1988). These early series were associated with the usual biases that one could expect from hospital-based studies. Depending on the geographical location of the hospital and the facilities provided in the special interests of the attending clinicians, it could also be argued that the proportions of lacunes could be artificially low because many of these have more minor neurological deficits and may not present to hospitals.

In spite of these limitations, hospital-based series gave us the first insights into the proportion of lacunar syndromes of all patients presenting with ischemic stroke. Estimates ranged from 11.2% (Lausanne, Switzerland) (Bogousslavsky et al., 1988) to 23.0% (Boston, USA) (Mohr et al., 1978) and 24.1% (Melbourne, Australia) (Chambers et al., 1983). In all of these studies the authors had a particular interest in lacunar syndromes and CT imaging was used in most cases.

Community-based studies quickly followed and a more precise estimate of the true proportion of lacunar syndromes was established (Gross et al., 1984; Ricci et al., 1989; Bamford et al., 1991; Norrving and Staff, 1991; Sacco et al., 1991). These estimates are shown in Table 27.1. In these studies imaging was also used, usually CT, to at least exclude other pathologies which may mimic lacunar syndromes, such as, small intracerebral hemorrhages and tumors.

Table 27.1

Incidence of lacunar stroke in community-based studies

Study	Total ischemic stroke (no. of patients)	Lacunar ischemic stroke (no. of patients)	Incidence of lacunar stroke[a]	Percentage
South Alabama (Gross et al., 1984)	138[b]	20	19.5[c]	14.5%
Oxfordshire (Bamford et al., 1991)	545	133	31.7[c]	24.4%
Italy (Ricci et al., 1989)	90	26	53.0[c]	28.9%
Mayo Clinic (Sacco et al., 1991)	1382	159	13.4[c]	11.5%
Australia (Anderson et al., 1994)	259	25	12.0[c]	9.7%
Norrving et al. (Norrving and Staff, 1991)	—	180[d]	26.6[d,e]	12.6%[f]

[a]per 100,000 persons per year; [b]includes recurrent stroke; [c]calculated from overall incidence figures; [d]pure motor stroke only; [e]age adjusted; [f]of all strokes.

In the series where radiological confirmation of the site of infarction was required (Minnesota, USA and Perth, Australia) the percentages were lower, probably because of the proportion in the brainstem, or the scan was performed too early to detect the infarct.

Hence, the incidence of lacunar stroke ranges from 12 to 53 per 100,000 persons per year which represents 9.7–28.9% of all ischemic strokes. Perhaps the simplest way to encapsulate the proportion based on information from the hospital and community-based studies is to give an overall estimate of about 20% ischemic strokes.

27.4. Pathogenesis and risk factors

This subject has always been an extremely contentious one, mainly because it has been so difficult to obtain adequate clinicopathological correlative studies and, until more recently, the difficulty in imaging small infarcts deep in the brain. It is useful to consider the evidence from a number of different perspectives, including pathological, risk factor, physiological and imaging studies. Each will be discussed in turn.

27.4.1. Pathological studies

As mentioned earlier, there have been relatively few pathological and clinicopathological correlative studies performed. Evidence comes from early studies performed in the great French school of neurology during the early part of the twentieth century (Reuling and Herring, 1899; Marie, 1901), and subsequently by Fisher and colleagues in Boston in the mid- and latter twentieth century (Fisher and Curry, 1965; Fisher, 1968, 1977, 1978a, b, 1979; Fisher and Caplan, 1971; Fisher and Tapia, 1987). Fisher, who studied a relatively low number of brains (18 in total), but performed meticulous histological analysis of thousands of sections sequentially along the penetrating arteries in the territory of lacunar infarcts, was able to infer that the mechanism of infarction was either lipohyalinosis (secondary to the effects of hypertension), micro-atheroma within the small vessel wall, lipping atheroma at the origin of the penetrating vessel at a larger vessel such as the middle cerebral or basal arteries or, in normal vessels, embolism remained a possibility (Fisher, 1965a, b, 1968, 1979; Fisher and Caplan, 1971). He was able to precisely locate the site of obstruction with reference to the dimensions of the infarct (Fig. 27.1). More recent evidence was provided by Lammie and colleagues who studied 70 brains and showed that lipolyalinosis and fibrinoid necrosis was rarely observed in the

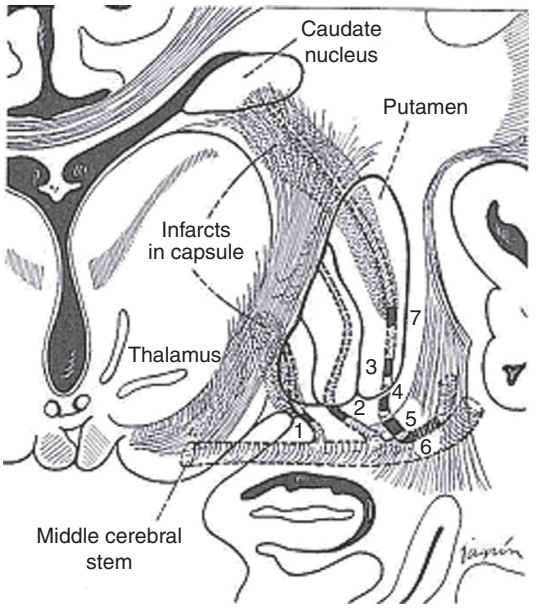

Fig. 27.1. Sites of vascular obstruction among nine cases in which serial sections were made along the length of the penetrating arteries (obstruction was seen in two cases at sites 1 and 7) (Fisher, 1979).

era of better blood pressure control (Lammie et al., 1997). Often classic risk factors were absent and they postulated that a variety of conditions that enhance small vessel permeability may contribute to the pathogenesis of small-vessel disease and lacunar infarction (Lammie et al., 1997).

27.4.2. Risk factor studies

Although simpler to perform than studies of pathology, again, surprisingly few well-performed risk-factor studies exist for patients with lacunar syndromes (Gandolfo et al., 1988; Tuszynski et al., 1989; You, 1993; Boiten and Lodder, 1995; You et al., 1995; Boiten et al., 1996). Of those performed, the traditional risk factors for stroke emerge, although there is some evidence that hypertension may be a more powerful risk factor than for other forms of ischemic stroke (You, 1993). However, not all investigators have uniformly supported this view (Fisher, 1965a, b, 1978a, b; Fisher and Cole, 1965; Chokroverty and Rubino, 1975; Donnan et al., 1982; Mohr, 1982; Yagnik et al., 1988; Tuszynski et al., 1989). The issue is complicated by the incorporation of risk factors in the definition of lacunar infarcts in some studies. In studies using risk-factor-free ischemic subtype definitions there was only a marginal excess of hypertension in lacunar versus non-lacunar infarcts (Jackson and Sudlow, 2005a). The possibility that different lacunar infarct entities exist based on the

presence of hypertension is interesting and deserves further investigation (Donnan et al., 1989).

Diabetes is a well-known cause of small-vessel disease and would therefore be more likely to be a risk factor for lacunar infarction. Whether it is a more potent risk factor than other forms of cerebral ischemia is debatable, although several investigators have found this to be so (Mohr, 1982; Donnan, 1984). In our own study (Donnan et al., 1989), as well as in other studies using risk-factor-free definitions (Jackson and Sudlow, 2005a), no difference for diabetes was found. The effect of diabetes, therefore, may be a nonspecific one, and may promote large- and small-vessel disease.

Smoking is also an established risk factor for lacunar infarction (Mohr, 1982; Donnan et al., 1989). In the majority of studies this also seems to be a nonspecific effect of ischemic stroke in general, although it is interesting that in our earlier study there was a trend toward an even high risk in lacunar syndromes (Donnan et al., 1989).

More recently, a number of studies on the genetics of lacunar infarction have identified a series of markers, including mitochondrial DNA 16189 T to C variant (Liou et al., 2004), polymorphism of the interleukin-6 gene (Revilla et al., 2002), endothelial nitric oxide haplotypes (Hassan et al., 2004a), and tissue plasminogen activator (tPA) polymorphism (Jannes et al., 2004), which seem to be associated distinctly with lacunar syndromes, more so than other ischemic stroke syndromes. Interestingly, the genetic marker which may be linked to insulin resistance was also found to be increased in lacunar stroke populations. Furthermore, formal tests of insulin resistance were also found to be abnormal in these populations compared to controls (Matsumoto et al., 1999). Other risk factors to emerge include inflammatory markers such as CRP, and elevated homocystine levels (Hassan et al., 2003, 2004b). Interestingly, Kazui et al. (2000) demonstrated that aortic atheroma was a risk factor for lacunar stroke. Whether this is because aortic atheroma is a marker of increased atheromatous load, including small penetrating vessels, or the arch atheroma may act as a source of embolism, is uncertain. However, Lodder et al. (1990) showed that patients with lacunar stroke had significantly fewer embolic sources than those with other forms of ischemic stroke.

27.4.3. Physiological studies

Given the importance of blood pressure inferred from the early findings of Fisher, and that lipohyalinosis was an important part of the lacunar infarction story, it is not surprising that investigators have focused on blood pressure levels and its control to try to unravel some of the mystery surrounding the vulnerability of these delicate penetrating vessels deep within the brain to blood pressure changes. Indeed, blood pressure levels have been reported to be higher in lacunar syndrome patients during the acute phases immediately post-stroke, and pulse pressure levels wider. There is also an emerging level of evidence that there is a loss of autoregulation of these penetrating vessels associated with lacunar infarcts, although whether this is a pre- or post-event phenomenon is unclear (Norrving, 1995; Molina et al., 1999).

27.4.4. Imaging studies

Like many other areas of stroke medicine, the application of modern imaging techniques to the lacunar infarction issue has significantly increased the general level of understanding of the disease process, although much still remains unknown. In earlier imaging studies using CT, better correlations between the clinical syndromes and small deep infarcts were able to be made and a re-evaluation of the broader ray of subcortical syndromes became more obvious (Donnan et al., 1982). In general, MRI is much more sensitive than CT, particularly for detecting lesions located in the brainstem (Donnan et al., 1993a). A higher proportion of patients presenting with lacunar syndromes are likely to have the clinically relevant infarct identified (about 75–90%) (Hommel, 1995). In general these infarcts are better seen on T2-weighted images than T1 images. It should be noted that occasionally lacunes are not detected by MRI, as demonstrated by Besson who reported a pontine lacune shown at autopsy that was not observed on MR images in vivo (Besson and Hommel, 1993b). It was shown that some lacunar syndromes were associated with multiple lacunar infarcts on MR Diffusion Weighted Imaging, thus suggesting that emboli could be responsible for a proportion of patients presenting with lacunar syndromes (Ay et al., 1999). In other studies multiple ischemic areas in single or multiple vascular territories suggestive of embolism was seen in 29–41% of patients with presumed lacunar infarcts (Caso et al., 2005; Wessels et al., 2005). However, even in patients with a pattern of multiple ischemic areas, an embolic source is not always found, and there remains a possibility that multiple lacunar infarcts may develop from other precipitating causes within a limited time window (Chowdhury et al., 2004; Caso et al., 2005).

Some lacunes were located in the distribution of the internal border zone region between penetrating vessels from the cortex and the ascending penetrators of

the striatocapsular region, thus suggesting that hemodynamic mechanisms may sometimes produce single or multiple lacunar infarcts (Waterston et al., 1990). In several interesting case reports, an ischemic penumbra was considered to be present, by showing the presence of a mismatch between perfusion-weighted image and diffusion-weighted image volumes (Chalela et al., 2003; Doege et al., 2003). These findings have, as yet, not been reproduced, probably because of the uncertainties surrounding the penumbral thresholds of perfusion-weighted images, particularly for small volumes such as these. However, the issue is an important one since it is now clear that a penumbral response may be mounted in white matter and the neurochemical ischemic cascade, which is glutamate- and excitotoxicity-dominated in gray matter, is somewhat different in white matter where sodium channel and adenosine/G protein-linked autoprotective mechanisms may be operative (Ransom et al., 1992; Ransom and Philbin, 1992).

There has been some debate about the upper size limit for lacunar infarcts. From autopsy studies the maximal lesion diameter of 15 mm has been considered a key criterion for imaging diagnosis (Fisher, 1965a). In cerebral autosomal dominant arteriopathy with subcortical infarcts and leukencephalopathy (CADASIL), a genetic disease exclusively affecting the wall of arteries less than 300 μm and leading to white matter demyelination and lacunar infarcts, a recent MRI study showed that 93% of all infarcts had a volume of less than 500 mm (Hauw, 1995); that is, well below the 15 mm diameter criterion (Herve et al., 2005). However, in the acute phase ischemic lesions due to lacunar infarcts may appear larger, and on diffusion-weighted MRI a majority of single ischemic lesions 15–20 mm in diameter had no other identified cause than single penetrating artery disease (Kang et al., 2003).

Wardlaw et al. (2001) studied nine patients in whom CT and MR had demonstrated a linear structure with density or signal features consistent with an occluded (or at least abnormal) perforating artery associated with the relevant lacunar infarct. They felt that the appearance might also have been caused by a leak of blood and fluid into the perivascular space around the artery, as in several patients the width of the tubular vessel-like structure (>1 mm in diameter) was greater than the expected width of a perforating artery (<0.8 mm in diameter). This interpretation was supported by the fact that the area of infarction was usually around the abnormal vessel, not at the end of it (Fig. 27.2) (Wardlaw et al., 2001). The possibility that a change in vascular permeability may predate or be associated with lacunar infarction had been raised earlier by Ma and Olsson (1993) in a pathological study. Boiten et al. (1993) were able to demonstrate that patients with multiple lacunes and leukoariosis appeared to have a

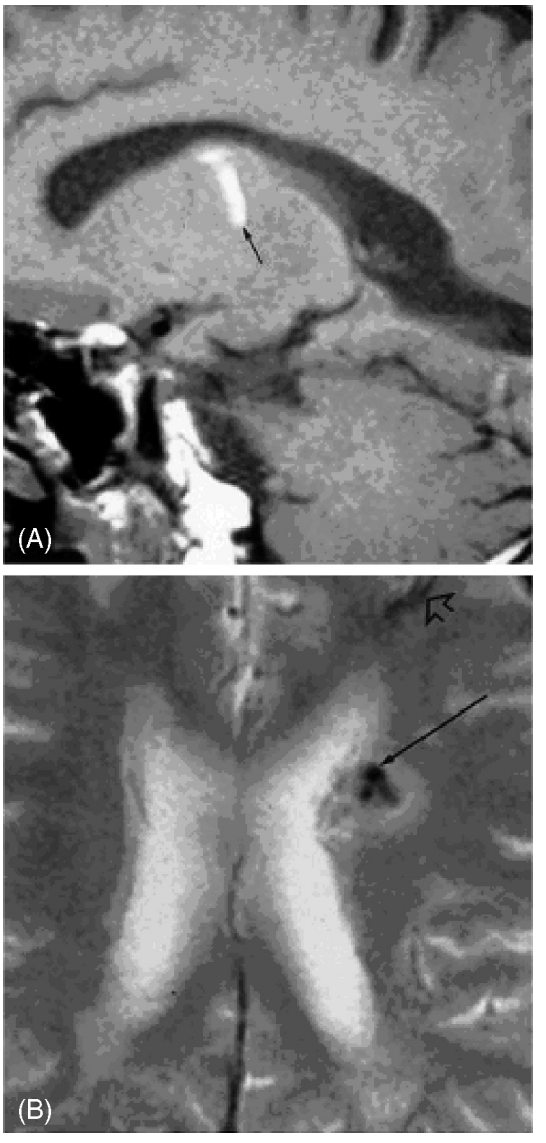

Fig. 27.2. (A) T1 sagittal magnetic resonance (MR) to the left of midline shows linear high signal consistent with blood products corresponding *(arrow)* with the abnormalities seen on axial imaging. On the immediately adjacent lateral slice (not shown) an area of low signal around this was more evidence consistent with infarction. (B) Gradient echo axial MR shows decreased signal consistent with hemosiderin lying centrally *(arrow)* within an area of increased signal *(arrowhead)* consistent with infarction. Note also on the MR images the area of previous hemorrhage in the left frontal cortex *(open arrow)* mild atrophy and some leukoariosis. There was also evidence of an old microhemorrhage in the right thalamus (not shown) and a further old cortical hemorrhage in the right occipital region (not shown) (Wardlaw et al., 2001).

somewhat different risk factor profile than those with single lacunar infarcts. Interestingly, Staaf et al. (2004) used diffusion-weighted imaging in patients with capsular warning syndrome (crescendo lacunar TIAs with high risk of early lacunar stroke; Donnan et al., 1993b) to infer that white-matter-related hemodynamic phenomena and/or spreading depression may be responsible for the frequency of the hemiplegic events.

From the above discussion it can be seen that lacunar infarction is usually due to in situ small vessel disease. The evidence that emboli from more distal sources such as the carotid artery, aortic arch, or heart are implicated in single penetrator lacunar infarcts causing lacunar syndromes in a significant proportion of patients is not strong (Norrving and Cronqvist, 1989; Lodder et al., 1990). Hence, in practical terms, the lacunar concept may be used to assist clinicians to predict the underlying pathogenesis and prognosis in individual cases. Evidence is emerging that deep penetrating vessels of the brain are unique and are influenced by such factors as hypertension, changes in blood–brain barrier permeability, loss of autoregulation, differing genetic profiles, and inflammation. When altered pathophysiologically by these factors, they may then be more vulnerable to systemic influences such as elevated homocysteine levels, hemodynamic factors or, very rarely, microemboli. The story is far from complete but a framework exists upon which to base further clinical and experimental studies.

27.5. Clinical syndromes

These have also been reviewed in a publication by Donnan and Yasaka (1998). The clinical expression of lacunar infarcts relates to the site of infarction and, to some extent, the mechanism of infarction; for example, lacunes of moderate size located in the posterior limb of the internal capsule are likely to produce a dense pure motor hemiplegia affecting the opposite side and involving face, arm, and leg equally. A smaller lacune in the pons may produce only modest ataxia and dysarthria. The tempo of onset may vary depending on the mechanism—slow if it is hemodynamic due to a high-grade stenosis of a small penetrating artery or more rapid (often smooth) in cases of in situ small-vessel thrombosis. As outlined earlier, Marie gave a remarkably accurate description of the main feature of lacunar strokes; that is, the involvement of long motor or sensory tracts without the presence of cortical signs of hemianopia. However, once again it was Fisher who clearly defined a series of "classic lacunar syndromes," which number five in all, although there is some overlap between them.

27.5.1. The classic lacunar syndromes

The advantage of defining and recognizing these syndromes in everyday clinical practice is the relatively high probability that these will be the clinical expression of underlying lacunar infarcts. The predictive value is probably higher for pure motor hemiparesis and pure sensory stroke than for the other syndromes.

27.5.1.1. Pure motor hemiparesis

Fisher described a series of 50 cases of "pure motor hemiplegia of vascular origin" (Fisher and Curry, 1965) and this remains the standard reference for the clinical features of lacunar infarctions in the internal capsule and basis pontis. Of the 50 cases, pathologic confirmation was achieved in nine: six cases of internal capsular infarction and three involving the basis pontis. The presence of a "pure motor" hemiplegia equally involving face, arm, and leg was redefined as "paralysis complete or incomplete of the face, arm and leg on one side, unaccompanied by sensory signs, visual field defect, dysphasia or apractagnosia." He emphasized the excellent prognosis of this syndrome (of 28 patients followed for 6 months, 15 showed almost complete recovery, 9 a moderate recovery, and 4 a complete recovery). In seven cases a tingling sensation was experienced in the face, arm, or leg at onset but no sensory loss was found on examination. Preservation of mental acuity "in the presence of a massive hemiplegia was a remarkable feature." Emotions were similarly preserved, although three patients cried easily and one had periods of uncontrolled laughter.

Given that this syndrome was described in the pre-CT scan era, it is not surprising that later investigators found that other small deep lesions could produce a similar clinical picture. Small cerebral hemorrhages, neoplastic metatastic deposits, and even cortical infarcts have been shown to produce pure motor hemiplegia (Chokroverty and Rubino, 1975; Donnan, 1984; Yagnik et al., 1988; Donnan et al., 1989). However it seems unlikely that cortical infarcts would be involved if cortical signs were carefully excluded and suggests that considerable license has been taken with the term "pure motor hemiplegia." With the introduction of CT as a screening mechanism to exclude other pathologies, the sensitivity and specificity for lacunar infarctions with pure motor hemiparesis remains high, in particular for syndromes involving the face, arm, and leg (Melo et al., 1992). The clinical syndrome of pure motor hemiplegia remains the most common and easily recognizable of all the lacunar states.

27.5.1.2. Ataxic hemiparesis

In 1965, Fisher and Cole described the lacunar syndrome of homolateral ataxia and crural paresis; 14 cases were presented all with cerebellar ataxia with weakness and pyramidal signs involving limbs of the same side (Boiten and Lodder, 1995). The leg was more severely affected than the arm. Nystagmus was seen in several cases. Pathologic confirmation in one case suggested that the lesion responsible was in the capsular corona radiate, although the presence of many other infarctions made this a dubious assumption. Fisher later altered the name of this syndrome to "ataxic hemiparesis" and described the pathologic findings in three cases where the lacune was limited to the basis pontis at the junction of the upper one-third and lower two-thirds on the side opposite the neurologic deficit (Tuszynski et al., 1989).

There are some earlier reports of descriptions of ataxic hemiparesis with pontine infarction (Revilla et al., 2002; Hassan et al., 2004a; Liou et al., 2004) and others have subsequently reported lacunes in the thalamus (Matsumoto et al., 1999; Hassan et al., 2003; Jannes et al., 2004). As for pure motor hemiparesis, some license has also been taken with the syndrome to include parietal ataxic hemiparesis (Hassan et al., 2004b). Hypoesthesia was reported as part of the ataxic hemiparesis syndrome by Fisher and Cole and "painful ataxic hemiparesis" has also been described with an infarct in the opposite thalamus shown on CT (Boiten and Lodder, 1995). Other variations include ataxic hemiparesis with contralateral trigeminal weakness (Kazui et al., 2000) and ataxic tetraparesis, both with infarcts in the basis pontis (Lodder et al., 1990). Interestingly, contralateral ataxia with crural paresis has also been described as a result of anterior cerebral artery territory infarctions (Molina et al., 1999).

27.5.1.3. Dysarthria–clumsy hand syndrome

The similarities between the syndrome of ataxic hemiparesis and the dysarthria–clumsy hand syndrome are quite striking and this was subsequently noted by Fisher (1967). In spite of this, the syndrome of dysarthria and clumsy hand continues to be described as a separate lacunar syndrome. The findings in the original case described by Fisher were of moderate facial weakness, slight weakness of the arm and leg, cerebellar dysmetria using the finger nose test, slowing of rapid repetitive movements of hand and foot, Babinski sign, and slight dragging of the leg (all on the right side), moderate dysarthria, and slight imbalance. Only one case came to autopsy and the findings were of a lacune in the uppermost 5 mm of the pons on the side opposite the clinical deficit. Although the differences between this syndrome and ataxic hemiparesis are small, the clinical findings and pathologic correlation appear to warrant a separate syndrome classification. Again, other sites of infarction causing the dysarthria clumsy hand syndrome have been reported, particularly the internal capsule (Fisher, 1965a; Gandolfo et al., 1988; You, 1993; Norrving, 1995; You et al., 1995).

27.5.1.4. Pure sensory stroke

The syndrome of pure sensory stroke has been one of the most difficult to delineate because of its purely subjective presentation and pathologic correlation in only one case in which the lacune was limited to the posteroventral nucleus of the thalamus (Boiten and Lodder, 1995). Two further cases have been reported although the latter involved a small slit hemorrhage in the posterior limb of the internal capsule and minimally the thalamus (Waterston et al., 1990; Hommel, 1995). Earlier reports involved the thalamocortical pathways and thalamus and Fisher later reported additional cases involving the thalamus (Fisher, 1982b). Hommel et al. (1989) reported pure sensory stroke due to a pontine lacune, while Sacco et al. (1987) noted proprioceptive loss that could be demonstrated in a patient with a thalamic lacune.

27.5.1.5. Sensorimotor stroke

A fifth lacunar syndrome of "sensorimotor stroke" with elements of both pure sensory and pure motor syndromes was the last classic syndrome to be described (Mohr et al., 1977). The initial description in the English literature was noted by Lapresle (Lapresle, 1978) who had described a similar case in the French literature in 1954 and 1960 (Garcin and Lapresle, 1954, 1960). The post mortem findings of a lacune involving both the internal capsule and thalamus suggested that these structures may occasionally share a common blood supply. Indeed, Dechambre was the first to describe a thalamocapsular lacune producing sensorimotor stroke in 1838, and in 1859 Turck also described well-documented post mortem thalamocapsular changes (Turck, 1859). CT observations of thalamocortical radiation infarcts have also been documented, as have small infarcts in the pons and medulla.

Unfortunately, sensorimotor stroke is another lacunar syndrome with which considerable license has been taken. Often cortical signs have not been adequately excluded so that larger deep infarcts, such as striatocapsular infarcts (Donnan et al., 1991), have also been included as possible causes, together with other pathologies described (Pullicino et al., 1980;

Rascol et al., 1982; Donnan et al., 1993a). To be of any practical use, the term sensorimotor stroke needs to be restricted to those syndromes with both sensory and motor involvement of the face, arm, and leg, with complete absence of cortical signs. With the assistance of modern neuroimaging techniques to exclude non-ischemic pathologies, this should result in a higher predictive value for the presence of a lacunar infarct in one of the sites described above.

27.5.2. Other lacunar syndromes

A variety of other lacunar syndromes have been described. It is our view that these are of more limited clinical use since the predictive value for lacunar infarction is extremely low. This, therefore, detracts from the usefulness of the lacunar concept for everyday stroke management. However, they are included for the sake of completeness and have been reviewed extensively (Besson and Hommel, 1993b). Descriptions include movement disorders such as chorea, dystonia, hemibalismus and balismus, asterixis, and parkinsonism. Other syndromes such as internuclear ophthalmoplegia, isolated third nerve palsies, Bendikt's syndrome, Claude's syndrome, pure motor hemiplegia plus sixth nerve palsies, horizontal gaze palsies, and one-and-a-half syndrome, have all been reported, as have vertical gaze palsies in association with aphasia due to thalamic infarcts and top-of-the-basilar syndrome. The mechanism of small infarcts in the brainstem producing many of these syndromes is likely to be varied. However, a recent diffusion-weighted MRI study of patients with small deep ischemic lesions showed that 40% of these infarcts were associated with a posterior circulation syndrome, suggesting that single penetrating artery disease may more often cause syndromes other than the classic ones (Seifert et al., 2005).

27.6. Transient events

Transient ischemic attacks (TIAs) were noted by earlier workers as a prelude to the development of lacunar stroke. As mentioned earlier, Marie stated: "The multiplicity of episodes, with a variable interval between them, is an essential characteristic of lacunar degeneration. Of my 50 cases, 32 had two or more previous episodes." Fisher, who is largely responsible for the modern understanding of the clinical features of lacunar disease, stated: "In our experience, a burst of frequent hemiplegic spells suggests the pure motor syndrome arising more likely in the capsule than the pons." This issue was taken further with a description of "lacunar TIAs" and the "capsular warning syndrome" to describe the occasionally spectacular burst of hemiplegic and/or hemianesthetic events that may predate the development of lacunar syndromes (Garcin and Lapresle, 1960; Donnan et al., 1993b, 1996; Oliveira-Filho et al., 2001; Staaf et al., 2004). The remarkable feature of this syndrome is the high risk of early stroke (40% within 10 days), much higher than a random sample of other forms of TIA (Donnan et al., 1996).

Apart from the dynamic aspects of lacunar TIAs and the capsular warning syndrome, can isolated lacunar TIAs be identified in a clinically useful way? In 1991, Hankey and Warlow (1991) defined a clinical template for lacunar TIAs as transient unilateral motor and/or sensory syndromes that involved at least two of three body parts (right face, arm, leg) in fully conscious, right-handed patients who attempted to speak during the episode and who reported no disturbance of language, cognitive, or visual function. In patients with presumed lacunar TIAs, an angiographic change of ipsilateral stenosis of 50% or greater was found in only 1 of 17 patients, but in 36 of 54 patients with presumed cortical TIAs. A reasonably accurate predictive mechanism of identifying patients with presumed lacunar TIAs was therefore established. Using a different approach, Kappelle et al. (1991) showed that, using a similar clinical template, a positive predictive value of lacunar symptoms of 0.74 (95% confidence interval [CI]; 0.59–0.87) and a negative predictive value of 0.61 (95% CI; 0.44–0.77) could be established for the CT identification of subcortical ischemia.

By using the following definition of probable subcortical ischemia, we found that of 1,093 consecutive patients with TIAs entering the Austin Hospital Stroke Unit, 14% were probably subcortical (involvement of face, arm, and leg simultaneously with no cortical signs such as neglect, dyspraxia, or dysphasia, or involvement of any two of these; and if the patient was examined during the event and/or a subcortical infarct was seen appropriate to the clinical findings) (Donnan et al., 1995).

A final question that needs to be answered concerning issues of transient lacunar events relates to interobserver reliability. Landi et al. (1992a) were able to show that the interobserver reliability of the diagnosis of lacunar TIAs was reasonably precise with an interobserver reliability kappa value of 0.88. For every clinical practice, therefore, one can be reasonably confident in the diagnosis of lacunar TIAs if face, arm, and leg are involved simultaneously and cortical symptoms can be satisfactorily excluded in right-handed people when the left hemisphere is

involved. When coupled with the dramatic presentation associated with capsular warning syndrome, it seems likely that this predictive value may be increased further. However, ancillary investigations such as CT and duplex of carotid arteries are useful to be assured that extracranial vascular disease is not involved in the pathophysiologic process.

27.7. Prognosis

Based on several studies with quite short follow-up periods there had been a common perception that prognosis after lacunar infarcts is generally favorable with good recovery in most patients, a low risk of recurrent stroke, and minimal risk for death (Gandolfo et al., 1986; Bamford et al., 1987, 1991; Giroud et al., 1991a, b; Hier et al., 1991; Sacco et al., 1991; Brainin et al., 1992; Landi et al., 1992b; Miyao et al., 1992; Boiten and Lodder, 1993; Nadeau et al., 1993; Anderson et al., 1994; Clavier et al., 1994; Sacco et al., 1994; Salgado et al., 1996; Samuelsson et al., 1996a; Petty et al., 2000; Kazui et al., 2001; Kolominsky-Rabas et al., 2001). However, this risk has been modified during the last few years after the publication of studies with longer periods of follow-up and also taking cognitive aspects into account (Yamamoto et al., 1998; Eriksson and Olsson, 2001; Staaf et al., 2001; De Jong et al., 2002; Yamamoto et al., 2002; Norrving, 2003).

The early risk of death is low, with a mean case fatality of 2.5% at 30 days and 2.8% at 1 year in the Norrving (2003) study. This should be no surprise because of the small lesion size, low risk of secondary complications, and low rates of cardiac co-morbidities. At 5 years about one-quarter of all patients with lacunar infarcts had died, a rate lower than for other subtypes of stroke (Jackson and Sudlow, 2005b), and in some studies even similar to the death rate in the general population.

However, studies with longer follow-up show an excess rate of death after lacunar infarcts after the first few years: after 10–14 years 60–75% of the patients had died (Eriksson and Olsson, 2001; Staaf et al., 2001). Long-term, about half of all deaths were cardiac and 20% due to stroke.

The rate of recurrent stroke at 1 year is about 8% followed by a rate of about 5% per year up to 4–5 years (Norrving, 2003; Jackson and Sudlow, 2005b). The 1-month risk of recurrent stroke is about two times greater in non-lacunar compared with lacunar infarct patients, but thereafter no significant difference in the rate of recurrent strokes has been documented (Norrving, 2003; Jackson and Sudlow, 2005b). Recurrent stroke of lacunar infarct subtype accounts for about half of all recurrent strokes, a proportion about twice as high as after non-lacunar stroke. Importantly, almost half of all recurrent strokes are of other subtypes.

The burden of classical vascular risk factors (hypertension, high 24-hour systolic blood pressure, diabetes, any cardio-embolic source) at baseline have been found to be predictors of recurrent stroke in several studies (Miyao et al., 1992; Kazui et al., 2001; Staaf et al., 2001; De Jong et al., 2002; Yamamoto et al., 2002; De Jong et al., 2003). Recurrent strokes also carry an increased risk of further recurrences (Soda et al., 2004). Interestingly, the burden of silent small-vessel disease on baseline neuroimaging has also appeared as a prognostic factor (De Jong et al., 2002; Yamamoto et al., 2002). The presence of intracranial stenosis in the parent artery, which is much more frequently associated with lacunar infarcts in Asians than in Westerners, also appears to carry an increased risk of recurrent stroke (Bang et al., 2004).

While patients with lacunar infarcts tend to have a more favorable functional outcome compared to other stroke subtypes, the proportion of patients who are dependent are not negligible: at 1 year, 18–33%; at 2 years, 36%; and at 3 years in 42% of patients (Bamford et al., 1991; Giroud et al., 1991a; Clavier et al., 1994; Samuelsson et al., 1996b; Petty et al., 2000). Besides age, diabetes, and severe initial stroke, baseline burden of small vessel disease have also been associated with a poor functional outcome (Samuelsson et al., 1996b; De Jong et al., 2002), suggesting that more advanced small-artery disease may limit the possibility of functional recovery of the brain after a small focal lesion.

Recovery of motor impairments with time is variable: whereas most patients improve considerably, a proportion of patients are left with marked deficits. Using color-coded diffusion tensor imaging, poor recovery has been linked to lesions centered on the corticospinal tract (often involving the basal ganglia), whereas those who had a good spontaneous recovery had smaller lesions located more anteriorly or medially (Lie et al., 2004).

While several studies have identified silent small-vessel disease as an independent predictor for post-stroke dementia (Leys et al., 2005), there are surprisingly few studies on cognition and dementia specifically in cohorts with lacunar infarcts. Early in the clinical course, neuropsychological examinations have shown few findings for simple tests, but impairments were found in tasks that were more demanding and required the effective use of several capacities (Van Zandvoort et al., 1998). Dementia was reported in 11% of patients 2–3 years after lacunar infarction

(Miyao et al., 1992; Samuelsson et al., 1996b), and 15% had dementia after 9 years in another study (Yamamoto et al., 2002). Development of dementia has often been reported in conjunction with recurrent strokes.

The importance of the co-existence of symptomatic lacunar infarcts, silent brain infarcts (most of which are small and deep) and white matter ischemic lesions for the prognosis of cognition as well as most other outcome measures after lacunar infarcts have only recently been recognized. These different entities of cerebral small vessel disease should not be regarded in isolation, as they appear to have additive or even synergistic effects. Interactions between the effects of lacunar infarcts and neurodegenerative processes like Alzheimer's disease have been demonstrated (Snowdon et al., 1997). Asymptomatic progression of cerebral small-vessel disease is at least twice as common as new strokes. After about 3 years almost half of all patients with lacunar infarcts have developed silent infarcts as well as progression of white matter ischemic lesions (Van Zagten et al., 1996).

27.8. Therapy

Until more recently lacunar syndromes have not been recognized as a separate stroke subtype as far as therapy is concerned. However, this is now changing with the increasing recognition by investigators that the underlying pathogenesis of lacunar syndromes is somewhat different to other ischemic stroke subtypes. Therefore, this may warrant a different approach to therapy. We will discuss studies in which it has been possible to dissect out lacunar syndromes and their response to therapeutic interventions as part of larger trials. Perhaps surprisingly, for both acute interventions and secondary prevention the response of lacunar syndromes seems to be similar to ischemic stroke generally based on the information available so far. There is an increasing amount of data becoming available concerning secondary prevention because of the "lacunarization" of trial populations. This is because patients with lacunar syndromes more often have modest neurological deficits and are hence ideal for long-term follow-up studies where repeated outpatient attendances are required.

27.8.1. Thrombolytic therapy

Interestingly, it was the first major study of thrombolysis to show improved clinical outcomes in which patients with small-vessel disease were considered as a subtype a priori. The investigators showed that the primary outcome of modified Rankin Scale score of 0–1 was similar for lacunar patients (when given 0.9 mg per kilogram tissue plasminogen activator (tPA) intravenously within 3 hours of symptom onset) and ischemic stroke patients (National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group, 1995).

27.8.2. Antiplatelet therapy

While antiplatelet agents have widely been used to prevent recurrence of ischemic stroke in general, there have been only two studies assessing the effects of antiplatelet agents on lacunar stroke (Gent et al., 1989; Yamaguchi et al., 1994). The Canadian American Ticlopidine Study (CATS) was a randomized, double-blind, placebo-controlled trial to assess the effect of ticlopidine (500 mg/day) in reducing the rate of subsequent occurrence of stroke, myocardial infarction, or vascular death in patients with recent atherothrombotic infarction (798) patients or lacunar stroke (274) (Gent et al., 1989). Ticlopidine reduced the relative risk of stroke, myocardial infarction, and cardiovascular death by 30.3% overall and, in the subgroup analysis, the relative risk reductions by ticlopidine were reported to be similar in patients with both atherothrombotic infarction and lacunar stroke. Unfortunately, detailed information was not provided for lacunar stroke alone. Two patients in the placebo group had subarachnoid hemorrhages, both fatal, and two patients in the ticlopidine group had primary intracerebral hemorrhages, one of which was fatal.

The Japanese Antiplatelet Stroke Prevention Study Group (JASPSG) study was a prospective, randomized, clinical trial of antiplatelet therapy in 610 patients with lacunar stroke (Yamaguchi et al., 1994). Patients were randomized to receive placebo or antiplatelet therapy. The antiplatelet therapy was aspirin, ticlopidine, or both. The dosage was decided by each attending physician and, as a result, more than 95% of patients in the antiplatelet group were given either ticlopidine (200 mg/day) or aspirin (most commonly less than 500 mg/day). Ticlopidine was more frequently used than aspirin (68% and 32% respectively). Twenty-three patients were given both drugs simultaneously for at least several months. After a follow-up period of 29 months (mean), it was reported that the annual recurrence rate of ischemic stroke was 3.4% in the 332 patients treated with antiplatelet agents, which was not significantly different from the 2.9% in the 278 patients in the placebo group. Patients treated with antiplatelet agents had a two-fold increased incidence of brain hemorrhage (0.8% per year with

ticlopidine and 0.4% per year with aspirin), but the difference was not statistically significant.

Any differences between these studies may relate to either drug dosage (higher in CATS) or to racial differences. The subjects in JASPSG were all Japanese, while 71% of subjects in CATS were Caucasian. This latter issue may also be important when considering cerebral hemorrhage rates. In controlled trials reported in Western countries, the incidence of brain hemorrhage is relatively low (0.4–1.2% of subjects) during antiplatelet therapy (American–Canadian Co-Operative Study Group, 1985; Swedish Cooperative Study, 1987; UK-TIA Study Group, 1988; Gent et al., 1989; Hass et al., 1989) but approximately 2% in patients treated with antiplatelet therapy in Japan. Whether this is because hypertensive arteriopathy (and therefore a higher tendency to bleed) is a more common cause of lacunar stroke in Japan is uncertain.

27.8.3. Anticoagulant therapy

Theoretically, because of the presumed mechanism of development of lacunar stroke (lipohyalinosis), it was considered that anticoagulation may be contraindicated, although there was no direct evidence for this. However, in a trial comparing warfarin and aspirin in the prevention of recurrent stroke (Mohr et al., 2001) there were no significant treatment-related differences in the frequency of, or time to, the primary end-point or major hemorrhage according to the cause of the initial stroke (56.1% of 2,206 patients studied had had previous small-vessel or lacunar infarcts).

27.8.4. Blood pressure lowering

In view of the fact that blood pressure is such an important risk factor for lacunar stroke, blood pressure lowering is potentially one of the most important secondary prevention strategies. Indeed, in the PROGRESS trial in which perindopril and indapamide were the blood pressure lowering agents among patients with TIA and minor stroke generally, lacunar stroke outcome events were reduced by 23% (95% CI, 7–44%), not different from other stroke subtype outcomes (Chapman et al., 2004). Since there is a need to test the blood pressure lowering hypothesis among lacunar syndrome patients specifically, investigators have launched the Secondary Prevention of Small Subcortical Strokes (SPS3) trial which is a factorially designed study involving blood pressure lowering and antiplatelet agents (325 mg aspirin versus 325 mg aspirin plus 75 mg clopidogrel) (Internet Stroke Centre, 2006).

27.9. Concluding remarks

There is no doubt that the term "lacune" has caused a great deal of confusion, particularly among those less familiar with the theoretical and historic basis of its origins. Some have suggested that the usefulness of the term has passed. While there is a reasonable argument for this, we believe that the term has become so solidly entrenched in the medical literature and common parlance that it would be difficult to eliminate entirely. A sensible approach may be to refer to syndromes that are due to the clinical expression of infarcts restricted to the *territory of a single penetrating artery*. Since, as discussed earlier, these are more likely to be due to in situ disease, an appropriate management strategy can therefore be adopted.

Once identified, how should patients with lacunar syndromes be managed? CT or MRI is essential to exclude other pathologies and, as far as possible, to identify the clinically relevant infarct. If an ipsilateral cervical bruit is heard, carotid duplex ultrasound could be reasonably used to exclude the rarely associated high-grade carotid stenosis (see earlier). If pre-existing or newly diagnosed hypertension is present, this should be treated appropriately with oral antihypertensive agents. Other risk factors should be screened for, particularly diabetes and smoking, and lifestyle factors should be addressed. The most appropriate antiplatelet agent for secondary prevention based on current evidence is aspirin at standard doses of 75–325 mg per day.

Once thought to be benign and rather innocent vascular lesions, lacunar infarcts should now be regarded as important markers of cerebral small-vessel disease with a high risk for an unfavorable outcome with time. The extent of asymptomatic small-vessel disease at the time of the first stroke has been shown to have important prognostic implications for almost all outcomes.

There is still a paucity of data concerning the mechanism of single penetrator vessel occlusion. There is hope that this may be rectified using the newer imaging techniques of MRA, transesophageal echocardiography, and transcranial Doppler with emboli detection. In all trials of acute intervention, patients with lacunar syndromes need to be identified a priori within the broader stroke group or specific trials for lacunar syndromes conducted. Whether the incidence of lacunar stroke is changing with time is uncertain, so there is a need for ongoing epidemiological studies to quantify this. Similarly, more trials of secondary prevention are needed with blood pressure, lipid lowering, and antiplatelet agents.

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Chapter 28

Hemorrhagic stroke syndromes: clinical manifestations of intracerebral and subarachnoid hemorrhage

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In developed countries, community studies from various centers indicate that approximately 70–80% of all strokes are ischemic, while approximately 20–30% are hemorrhagic (10–20% intracerebral and 5–10% subarachnoid hemorrhage) (Tanaka et al., 1981; Ashok et al., 1986; Foulkes et al., 1988; Ueda et al., 1988; Ward et al., 1988; Broderick et al., 1989; Bamford et al., 1990; Ricci et al., 1991; Kase et al., 2004), although a recent systematic review by Keir et al. (2002) suggested that stroke epidemiology studies have underestimated the frequency of intracerebral hemorrhage. Therefore, hemorrhagic stroke syndromes, which will be described in this chapter, comprise the clinical manifestations of intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH). Although hemorrhagic stroke is not as common as ischemic stroke, and recurrence of hemorrhage in 1-month survivors is less common than in ischemic stroke (Fogelholm et al., 1992; Hill et al., 2000), its consequences can be devastating and even fatal.

The introduction of computerized tomography (CT) has revolutionized the diagnosis of ICH and SAH. Clinical criteria formerly used to make the diagnosis, particularly for ICH (Fisher et al., 1965; Walker et al., 1981) are now reserved only for severe cases, and are no longer applied to diagnose mild or moderate forms (Nagayama et al., 1991). CT scanning can easily delineate the location, size, and severity of the hemorrhage. However, CT or magnetic resonance imaging (MRI) is not always readily available immediately after the onset, and furthermore, it is important to avoid overlooking possible complications in some patients. Therefore, the general clinical and specific neurological manifestations in each type of hemorrhage will be covered here.

28.1. Clinical manifestations of intracerebral hemorrhage

28.1.1. General manifestations

The onset of clinical manifestations of ICH is, in the majority of cases, abrupt without any prodromes. It develops while the patient is awake and active (such as at the lavatory, in the bath, in the office, standing or walking, during eating and drinking, during exciting activities including sexual intercourse, and so on). It rarely occurs during sleep, but amounted to less than 10% in our series of 179 ICH patients (Nagayama et al., 1992).

Clinical manifestations of ICH can be divided into general manifestations and those that are dependent on the location of the hematoma. Patients with a large hematoma usually show headache, vomiting, decreased level of consciousness and so on as a result of increased intracranial pressure and brain edema (Thiex and Tsirka, 2007), and direct compression or distortion of the brainstem and thalamic reticular activating system (Andrews et al., 1988). It is important to note that the severity of ICH is generally becoming less marked than in previous years, possibly because of the increasingly tight management of hypertension, the largest risk factor for ICH, although other risk factors for ICH such as cerebral amyloid angiopathy (CAA), cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), use of

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anticoagulants or thrombolytics and so on, seem to be increasing (Badjatia and Rosand, 2005; Ragoschke-Schumn et al., 2005; Thanvi and Robinson, 2006). Therefore, the bedside differential diagnosis of ICH from ischemic stroke has become more difficult if CT or other neuroimaging techniques are unavailable.

28.1.1.1. Headache

It has generally been believed that headache is a prominent feature in ICH, but it has been shown that only about half (in our series) or less than half (Fisher, 1961) of patients had headache at the onset of ICH, and it was usually mild and fleeting (Fisher, 1961). Therefore, if a patient complains of severe, sudden headache at the onset, complication of SAH should also be considered. The headache in ICH may become more severe with the passage of time (Kameyama et al., 1988). When headache is present, it is lateralized from the onset to the side of the hematoma in almost 30% of cases (Omae et al., 1989).

28.1.1.2. Vomiting

Vomiting is a relatively common clinical sign in ICH, particularly in patients with cerebellar hemorrhage, in whom the onset of stroke may be marked by severe vomiting, or in patients in whom hemorrhage extends to the ventricles or subarachnoid space. It occurred in 51% of patients in the Harvard Stroke Registry (Mohr et al., 1978) and 42% in our series.

28.1.1.3. Disturbances of consciousness

The severity of disturbance of consciousness, which may differ depending upon the location and stage of hemorrhage and the period after onset, is an important indication of the severity of stroke. Since there are many conflicting definitions of consciousness disturbance, the apparent frequency varies from report to report. In our series, disturbance of consciousness, which we defined as conditions more severe than disorientation or somnolence, was observed in 79% of ICH, which was more frequent than in patients with atherothrombotic or lacunar infarction. However, it was also observed in 73% of patients with cardio-embolic stroke in our hospital, suggesting that impairment of consciousness level is not useful for differential diagnosis of ICH from cardio-embolic stroke.

The relationship between the severity of consciousness disturbance at onset and the degree of functional recovery at 3 months in 171 elderly (more than 60 years old) patients with ICH was investigated by Kameyama et al. (1988). In patients showing alertness, confusion, delirium, or senselessness, functional recovery was usually good, but those with severe disturbance showed little or no functional recovery after 3 months. Generally speaking, patients who remain in coma for more than 24 hours have a very poor prognosis.

28.1.1.4. Change of vital signs at onset

Hypertension of various degrees is nearly always observed, even in patients without severe high blood pressure before onset. Usually patients have other manifestations related to high blood pressure, such as cardiac enlargement, retinal arteriolar change, renal impairment, and so on.

Kameyama et al. (1983) have reported a series of patients in whom the value of blood pressure was coincidentally measured at 7 days before onset of ICH; the blood pressure was elevated from 166 $\pm$ 21 mmHg (mean $\pm$ SD) to 212 $\pm$ 28 mmHg (systolic) and from 89 $\pm$ 13 to 108 $\pm$ 19 (diastolic) within 12 hours after the onset of ICH in 70% of these patients, although it was not established whether the elevation occurred immediately before the onset of hemorrhage or after. They also suggested that a systolic blood pressure greater than 200 mmHg immediately after the onset of stroke is seen more frequently in patients with ICH than in those with cerebral infarction. However, it should be emphasized that even in cerebral infarction, a slight to moderate degree of hypertension has been observed in almost 50% of patients in our institute. Furthermore, recent advances in neuroimaging techniques have enabled us to detect even small hemorrhages. Therefore, bedside diagnosis of ICH based only on these clinical findings is not recommended.

Body temperature is usually elevated slightly in ICH, and patients in the terminal stage of ICH may show severe hyperthermia (so-called terminal hyperthermia) without elevation of pulse rate, probably due to impairment of the hypothalamus. In this case, rectal measurement of temperature may be recommended. Abnormal respiration, such as bradypnea, Cheyne–Stokes respiration, hyperventilation, ataxic respiration and so on, is also present.

28.1.1.5. Time course of general manifestations

Usually the neurological symptoms of ICH begin abruptly, and develop steadily and smoothly over a period ranging from several minutes to less than 72 hours. In our series, 66% of the ICH showed maximal symptoms within 1 hour of onset.

Active bleeding in ICH is reported to continue for less than 2 hours (Herbstein and Schaumburg, 1974; Ojemann and Mohr, 1976; Ferro, 2006). Clinical deterioration occasionally observed after onset is attributable to the development of brain edema (Hoff and Xi, 2003), but generally not to continued bleeding.

Nevertheless, in exceptional cases, clinical deterioration correlates with worsening CT findings, which may show an enlargement of hematoma upto 72 hours or longer after admission (Fig. 28.1) (Omae et al., 1989; Nagayama et al., 1992; Brott et al., 1997). These cases indicate that persistent severe hypertension or marked fluctuation of blood pressure may play a role in prolonged bleeding or rebleeding, and therefore particular attention should be paid to the management of hypertension during the acute phase.

28.1.2. Location of primary ICH

Primary intracerebral hemorrhage is classified on the basis of location into five types: putaminal (lateral type), thalamic (mesial type), hemispheric (lobar type), cerebellar, and brainstem. Lateral type and mesial type are divided according to whether the hemorrhage is lateral or mesial to the internal capsule. In patients with large hemorrhage that cannot be clearly defined as either putaminal or thalamic, the term "combined" or "mixed" is used. Table 28.1 demonstrates the incidence of ICH according to the site of the lesion in a series confirmed by CT.

Earlier reports based on diagnosis confirmed at autopsy may be biased, because they would have included severe cases only. Therefore, Table 28.1 shows reports in which diagnosis was supported by CT observations. Putaminal hemorrhage was most frequent, followed by thalamic and hemispheric hemorrhage, although Diamond et al. (2003) indicated that the most common sites of ICH are lobar.

28.1.3. Clinical manifestations according to the location of hematoma

The dependence of characteristic clinical features on the location of hematoma was examined in detail by Fisher et al. (1965) based on autopsy cases and partially on operated cases. However, the advent of CT scanning has enabled us to confirm even small hemorrhages and the recent trend towards strict management of hypertension has resulted in a reduction of the severity of cerebral hemorrhage.

We previously selected 179 patients with primary and first-ever ICH within 3 days of onset among 413 patients with ICH diagnosed by CT scanning and analyzed their clinical manifestations (Nagayama et al., 1991). Based on the clinical symptoms and CT findings of these patients, together with data from many other reports, the clinical manifestations of ICH at different locations can be summarized as follows.

28.1.3.1. Putaminal hemorrhage

The most common origin of putaminal hemorrhage is thought to be a lateral branch of the lentriculostriate arteries (named the artery of cerebral hemorrhage by Charcot and Bouchard (1868)). The clinical manifestations of more substantial putaminal hemorrhage are mainly due to compression of the surrounding tissues, such as the internal capsule, due to the hematoma itself

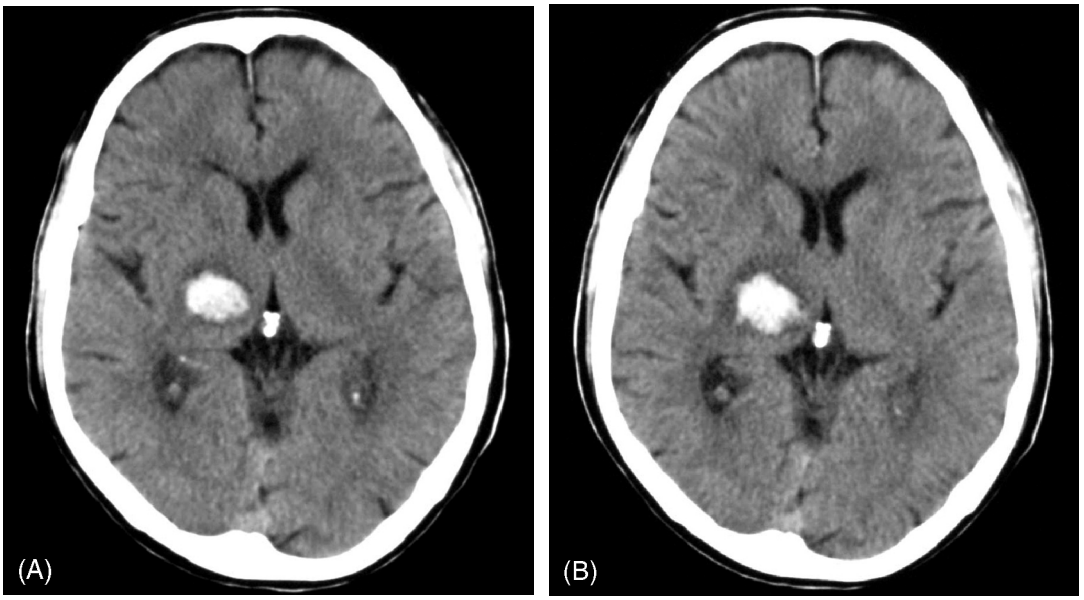

Fig. 28.1. (A) Finding of a 63-year-old male with thalamic hemorrhage on the day of hemorrhage. (B) CT finding on the next day.

Table 28.1

Frequency of various locations of ICH confirmed by CT scan

Authors	Putamen	Thalamus	Combined	Lobar	Brainstem	Cerebellum	Others*	Total
Wiggins et al. (1978)	18 (56)	3 (1)		5 (16)	1 (3)	5 (16)	—	32
Weisberg (1979)	222 (92)			20 (8)	—	—	—	242
Shizuka et al. (1980)	131 (54)	88 (35)		14 (6)	11 (4)	5 (2)	—	249
Herold et al. (1982)	44 (61)			27 (38)	1 (1)	—	—	72
Nagayama et al. (1991)	60 (34)	39 (22)	30 (17)	21 (12)	16 (9)	13 (7)	—	179
Sawada (1993)**	292 (39)	233 (31)		109 (15)	67 (9)	38 (5)	5 (1)	744
Kase et al. (2004)***	34 (34)	24 (24)	4 (4)	24 (24)	6 (6)	7 (7)	5 (5)	100

*Others include caudate and primary ventricular hemorrhage.
**Including reattack cases.
***Cases probably confirmed by CT scan.
( ): percentage.

and development of edema. Therefore, the severity of symptoms depends on the size of the hematoma (Gotoh, 1990).

28.1.3.1.1. Motor and sensory deficits

Hemiplegia and sensory deficits are most commonly seen, with motor deficits being predominant. Hemiplegia is observed in almost all patients (though not 100%) with putaminal hemorrhage. If hemorrhage occurs near the anterior limb of the internal capsule, motor paresis is relatively mild and resolves in most cases. By contrast, if hemorrhage involves the posterior limb, severe hemiplegia with hemisensory impairment is frequent.

Hemiplegia may equally involve the upper and lower extremities or sometimes may be more severe at the upper extremity on the opposite side to the hematoma, and, if the internal capsule is severely damaged, the hemiplegia may become flaccid. Although some patients may show pure motor hemiparesis resembling one of the lacunar syndromes, hemisensory impairment on the opposite side to the lesion is seen in about 80–90% of patients. Usually hemisensory impairment involves all modalities.

28.1.3.1.2. Ocular manifestations

Furthermore, patients with putaminal hemorrhage show homonymous hemianopsia of the opposite side, when the hematoma extends posteriorly and involves the optic radiation, and also exhibit paralysis of conjugate gaze mainly to the opposite side of the lesion, resulting in conjugate deviation of the eyes towards the affected side. It should also be emphasized that in rare instances, paralysis of conjugate gaze to the ipsilateral side of the lesion may be observed. In the case of development of uncal or central herniation, ipsilateral or bilateral dilated pupils with respiratory abnormalities may occur. Those signs always indicate a poor prognosis.

28.1.3.1.3. Higher brain dysfunction

In patients with lesions on the dominant side, aphasia is a common occurrence. On the other hand, in patients with lesions on the non-dominant side, hemispatial agnosia, constructional apraxia, dressing apraxia, anosognosia, and so on may occur.

28.1.3.1.4. Consciousness disturbance

One of the important manifestations of putaminal hemorrhage is impairment of consciousness. In patients with hematomas of moderate to large size, consciousness level is usually impaired, but unconsciousness at onset is not so common in recent putaminal hemorrhage (less than 40% in our series). A typical clinical course would be a gradual worsening of the above manifestations, including decreased consciousness level, in the minutes or hours following onset. A large hematoma produces coma and bilateral extensor plantar reflexes due partially to increased intracranial pressure and partially to the mechanism of diaschisis (Meyer et al., 1970).

28.1.3.1.5. Involuntary movement

Patients with a very small putaminal hemorrhage located within the putamen may rarely show involuntary movement, such as hemichorea (Jones et al., 1985), athetosis, or dystonia, but are usually asymptomatic.

28.1.3.1.6. Prognosis

Intraventricular extension of putaminal hemorrhage results in a poor prognosis (Gotoh, 1990). Hier et al.

(1977) reported that 8 of 24 patients had an intraventricular extension, which proved fatal in most of them.

28.1.3.2. Thalamic hemorrhage

The typical clinical findings of thalamic hemorrhage are rather similar to those of putaminal hemorrhage.

28.1.3.2.1. Motor and sensory deficits

The main manifestations are hemiplegia and hemisensory impairment. Hemiplegia is attributable to compression from the thalamic side at the internal capsule due to the hematoma in the thalamus and the related edema. In some cases, sensory deficits are more severe and develop earlier than the motor deficits in patients with thalamic hemorrhage, although this is not so useful for the differential diagnosis of thalamic hemorrhage from putaminal hemorrhage. Patients may complain initially of numbness or tingling of the contralateral face and limbs preceding the onset of weakness and depressed consciousness (Fazio et al., 1973). Sometimes the distribution of sensory impairment shows so-called "cheiro-oral topography (syndrome sensitif à topographie cheiro-orale)," and if a small hematoma is located in the thalamus, the patient may show sensory impairment only.

Patients with thalamic hemorrhage may have severe pain or a burning sensation on the contralateral side of the body (thalamic pain) a few weeks or several months after onset. It was reported that thalamic pain occurs more often in patients with lesions on the non-dominant side than in those with lesions on the dominant side (Kameyama et al., 1988).

28.1.3.2.2. Involuntary movement

Together with pain, patients may have mild or moderate hemiparesis, cerebellar ataxia, and choreoathetoid involuntary movements (anterolateral thalamic syndrome). Unusual and restless hand position (thalamic hand) may also be seen in the chronic stage of thalamic hemorrhage.

28.1.3.2.3. Higher brain dysfunction

Patients with lesions on the dominant side may show a peculiar aphasic syndrome, manifesting perseveration, palilalia and/or paraphasia, although this may be transient or fluctuating (Mohr et al., 1975; Reynolds et al., 1978). On the contrary, patients with lesions on the non-dominant side may show asomatognosia.

28.1.3.2.4. Ocular manifestations

The characteristic oculomotor findings are an important manifestation of thalamic hemorrhage, and may be the only symptom that is different from those in putaminal hemorrhage. Downward deviation of the eyes is observed at the onset of thalamic hemorrhage, especially in severe cases. This is attributable to the downward extension of hematoma and the involvement of the midbrain. The patient looks as if he or she is "peering at the tip of the nose." The eye on the side opposite the hemorrhage may be dislocated medially and downward, showing skew deviation (Fig. 28.2). Complete paralysis of vertical gaze, both upwards and downwards (Parinand syndrome), together with miosis or Horner's syndrome, anisocoria, loss of light reaction, and so on, may be observed, owing to the effects of the hematoma and surrounding edema on the midbrain tectum (Christoff, 1974; Walshe et al., 1977; Barraquer-Bordas et al., 1981). Moreover, forced conjugate deviation to the ipsilateral or contralateral side of the lesion (conjugate deviation to the contralateral side was designated "wrong-way" eye deviation by Fisher (1967)) may also occur (Walshe et al., 1977; Barraquer-Bordas et al., 1981). However, the frequency of these horizontal conjugate deviations was less than 20% in our series, which is far less than in putaminal hemorrhage.

28.1.3.2.5. Consciousness disturbance

Decreased level of consciousness is also a common finding in thalamic hemorrhage. States more severe than delirium or confusion were observed in almost 50% of our series. Thalamic hemorrhage may rupture into the ventricular system if it occurs near the ventricles. In this case, focal neurologic signs are not prominent, as in the case of caudate hemorrhage, and this situation is often indistinguishable from SAH.

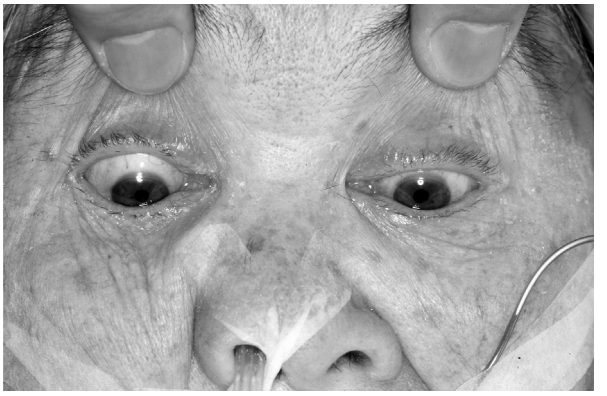

Fig. 28.2. Medial and downward dislocation of bilateral eyeballs, particularly on the right eye (skew deviation) in a 75-year-old female with right thalamic hemorrhage.

28.1.3.3. Combined (mixed) type hemorrhage

The diagnosis "combined or mixed hemorrhage" should not be used if the origin of bleeding is known. However, in some severe cases, it may be impossible to decide whether the hemorrhage originates from the putamen or thalamus. Combined hemorrhage shows a high incidence of consciousness disturbance at onset (73% in our series), repeated vomiting (64%), anisocoria, loss of light reaction, and conjugate deviation to the ipsilateral side of the lesion, as well as hemiplegia and hemisensory impairment.

28.1.3.4. Lobar (hemispheric or subcortical) hemorrhage

Lobar hemorrhage, which may be called hemispheric or subcortical hemorrhage, may (in contrast to putaminal and thalamic hemorrhages) have a specific etiology other than hypertension, such as aneurysm, amyloid angiopathy, arteriovenous malformation, use of anticoagulants, liver disorder, collagen disease, brain tumor, and so on. Therefore, etiological diagnosis is also important to manage cases of lobar hemorrhage. The frequency of lobar hemorrhage at different locations is not well established. It may occur in any part of the cerebrum, particularly the cerebral subcortices, but is more common in the parietal lobe (Weisberg, 1985), occipital lobe (Ropper and Davis, 1980) or parietotemporal lobe (Kase et al., 1982).

28.1.3.4.1. Clinical characteristics according to the etiology

28.1.3.4.1.1. Hypertensive lobar hemorrhage

As described by Broderick et al. (1983), hypertension is also an important etiologic factor for lobar hemorrhage, particularly in the elderly, although it is less frequent than in other hemorrhages (Kase et al., 1982). The differential diagnosis with amyloid angiopathy is important, but if the patient has hypertension before the onset of hemorrhage, it should be considered as a cause.

28.1.3.4.1.2. Lobar hemorrhage due to amyloid angiopathy

Usually this is seen in patients more than 70 or 80 years old (Vonsattel et al., 1991). The hematoma is often huge, irregularly shaped, and multiple. Recurrence is common. Sometimes dementia may precede the onset of hemorrhage (Gilles et al., 1984).

28.1.3.4.1.3. Lobal hemorrhage due to cryptic vascular malformation

This is seen mostly in males at 30–50 years of age. It may be familial (Rigamonti et al., 1988). The vascular malformation may be difficult to identify after the onset of hemorrhage, because it may be destroyed by the hemorrhage itself.

28.1.3.4.1.4. Lobar hemorrhage due to rupture of aneurysm

In cases such as aneurysmal rupture of the middle cerebral artery, hemiplegia and/or aphasia, together with signs and symptoms of SAH, are observed. To confirm aneurysmal rupture, cerebral angiography is necessary.

28.1.3.4.1.5. Lobar hemorrhage due to anticoagulants and antiplatelets

Use of tPA, heparin, warfarin or antiplatelets may induce a large hematoma in the subcortex and so on (Kase et al., 1985, 1990; NINDS t-PA Stroke Study Group, 1997; Ariesen et al., 2004; Gorelick and Weisman, 2005; Trouillas and von Kummer, 2006). The prognosis of such hemorrhages is very poor.

28.1.3.4.1.6. Lobar hemorrhage related to brain tumor

CT or MRI is essential to diagnose this hemorrhage. Severe edema around an irregularly shaped hemorrhage with abnormalities may be indicative of a brain tumor. Patients may show papilledema at the onset of hemorrhage.

28.1.3.4.1.7. Lobar hemorrhage related to hemological diseases

Leukemia, aplastic anemia, thrombocytopenia, liver disorders and so on may also cause lobar hemorrhage.

28.1.3.4.2. General manifestations of lobar hemorrhage in the acute stage

Clinical manifestations of lobar hemorrhage in the acute stage depend on the size, location and speed of extension of the hematoma. Common manifestations are symptoms due to increased intracranial pressure and meningeal irritation, and convulsion.

28.1.3.4.2.1. Headache

Headache generally precedes, but rarely develops after the onset of, hemorrhage (Ropper and Davis, 1980). The frequency of headache may vary according to the size and location of hematoma, and reported frequencies range from 25% (Sawada, 1986) to 40–50% (Mohr et al., 1978; Ropper and Davis, 1980). The site of headache is related to the location of hematoma, and is usually near the location of the hematoma.

28.1.3.4.2.2. Nausea and vomiting

Forty percent of patients may develop nausea and headache, particularly in the case of rupture into the subarachnoid space or ventricles.

28.1.3.4.2.3. Early seizure

The development of early seizure in lobar hemorrhage (within 3 days after onset) is more frequent than in

other hemorrhages, probably due to the location of the hematoma, and less severe consciousness disturbance (Faught et al., 1989). The frequency of early seizure is between 6% and 36%, depending on the location of the hematoma (Weisberg et al., 1991). Seizure develops earlier with smaller than with larger hematoma.

28.1.3.4.2.4. Consciousness disturbance
Deep coma is rare in patients with lobar hemorrhage. The consciousness level is alert in many cases, and even if consciousness is disturbed (14% in our series and 24% in Sawada's series (1986)), the disturbance is rather slight.

28.1.3.4.2.5. Focal neurological manifestations
Hemiplegia, hemisensory impairment, aphasia, hemianopsia, and so on, may be observed depending on the location of the hematoma. The clinical manifestations of lobar hemorrhage in each are similar to those of embolic stroke in the corresponding location (Ropper and Davis, 1980). Although the observation of clinical manifestations is important, final confirmation of the diagnosis should be based on CT scan or MRI. However, the physician should always consider the differentiation of hemorrhagic infarction from lobal hemorrhage.

28.1.3.4.2.5.1. Frontal subcortical hemorrhage Frontal headache, hemiplegia, gaze palsy, conjugate deviation and a slight degree of consciousness disturbance are characteristic findings. Patients may show psychological symptoms, such as transient abnormal behavior, poriomania, anxiety, or excitement. Neurological examinations reveal forced grasping, incontinence, catalepsy, and so on. Aphasia is rare and visual field defect is not observed.

28.1.3.4.2.5.2. Temporal subcortical hemorrhage Weisberg et al. (1990) classified temporal subcortical hemorrhage into temporal-frontal, temporal-ganglionic, temporal-parietal, posterior-temporal, and inferior-basal temporal according to the location and direction of the extension of the hematoma. Temporal subcortical hemorrhage on the dominant side usually produces aphasia. If the hematoma extends forward, Broca's aphasia may develop, and if backward, Wernicke's aphasia may develop. Hemorrhage on the non-dominant side may produce delirium or abnormal behavior without any other focal neurological symptoms. If the hematoma extends inward or upward, hemiplegia may be prominent and backward visual disturbance (hemianopsia or quadranopsia) will develop. Temporal headache or retroauricular pain may appear at a location corresponding to that of the hemorrhage.

Vaquero et al. (1988) reported a very rare left temporal ICH due to rupture of AVM, showing ipsilateral hemiparesis without facial involvement, possibly as a consequence of secondary sensory–motor area damage. Furthermore, a case of right temporal lobe hemorrhage in which ipsilateral facial pain was the initial feature was also reported (Ghougassian and Beran, 2000).

28.1.3.4.2.5.3. Parietal subcortical hemorrhage If the hemorrhage is on the dominant side, patients may develop aphasia (Wernicke's aphasia, conduction aphasia, or global aphasia) (Tanaka et al., 1986). If it is on the non-dominant side, hemispatial neglect, constructional apraxia, dressing apraxia, asomatognosia, motor impersistence, sensory extinction, astereognosis and so on may variously develop. Hemiplegia, hemisensory impairment and visual disturbance may develop, but their frequency is not high.

28.1.3.4.2.5.4. Occipital subcortical hemorrhage Patients with occipital subcortical hemorrhage may complain of ipsilateral retro-ocular or peri-orbital pain on onset. The occurrence of hemianopsia is essential, but may not be complained of by patients (Anton's syndrome). Agraphia and alexia are rather common, and amnesia may develop in cases of dominant side hemorrhage.

28.1.3.4.3. Differences of clinical manifestations and prognosis between lobar and ganglionic hemorrhage

In summary, the differences of clinical manifestations are less severe but more frequent headache, less hemiplegia, and less pre-existing hypertension in lobar hemorrhage than in basal ganglionic (putaminal and thalamic) hemorrhage (Massaro et al., 1991). Unlike putaminal or thalamic hemorrhage, the prognosis of lobar hemorrhage is good (Kase et al., 1982; Tanaka et al., 1986), except where the volume of hematoma is more than 40– 80 ml (Radberg et al., 1991).

28.1.3.5. Brainstem hemorrhage

Brainstem hemorrhage accounts for about 3–9% of ICH (Table 28.1). The brainstem includes the midbrain (mesencephalic), pons, and medulla, but the frequencies of midbrain and medullary hemorrhages are very small. Pontine hemorrhage mostly occurs at the pontine tegmentum (particularly the lower pontine tegmentum) of one side and expands to the tegmentum of the opposite side, the fourth ventricles, or basis pontis.

28.1.3.5.1. General considerations

Clinical pictures vary depending on the size and location of hematoma, as is the case with other kinds of ICH. Development of CT has enabled us to diagnose small, nonfatal brainstem hemorrhage. Before the CT era, information on the clinical pictures of brainstem

hemorrhage had been obtained from patients with large hemorrhage verified by post mortem examination, and it had been considered that brainstem hemorrhage is invariably fatal. Therefore, early reports of symptomatology apply only to patients with severe hemorrhage. However, it is now clear that there are many patients with nonfatal brainstem hemorrhage who show only very slight symptoms.

28.1.3.5.2. Clinical manifestations according to the location of hemorrhage

28.1.3.5.2.1. Midbrain (mesencephalic) hemorrhage
Hypertensive midbrain hemorrhage is rare (Durward et al., 1982; Morel-Maroger et al., 1982; Posadas et al., 1994). Most midbrain hemorrhage is secondary or an extension from thalamic hemorrhage or pontine hemorrhage. The main causes of primary midbrain hemorrhage are leukemia, cavernous hemangioma or small arteriovenous malformation. However, hypertensive midbrain hemorrhage also exists. Clinical manifestations of midbrain hemorrhage include Weber's syndrome, Benedikt's syndrome, reversible third nerve nuclear syndrome (Gaymard et al., 1990), isolated unilateral infranuclear third nerve palsy (Fig. 28.3) (Ooki et al., 1994), Holmes-like tremor (Walker et al., 2007), and so on.

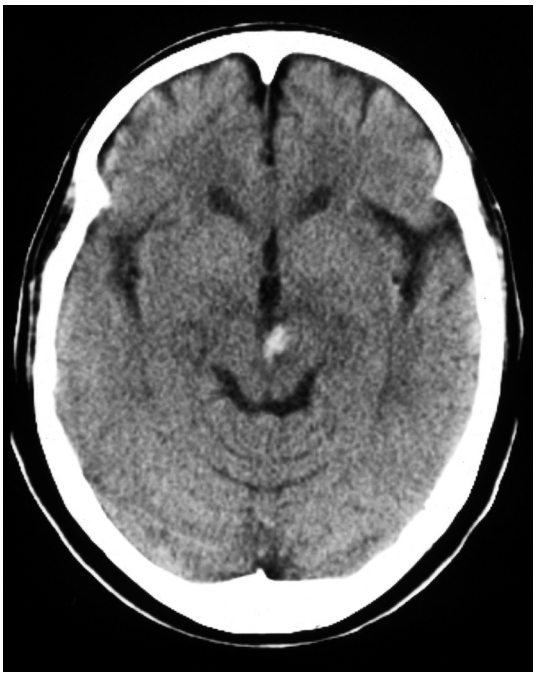

Fig. 28.3. Midbrain hemorrhage. CT finding of a 67-year-old female presenting with only eyelid ptosis and infranuclear oculomotor palsy with pupil dilation on left side. No other neurological abnormalities were detected in this case.

28.1.3.5.2.2. Pontine hemorrhage
Kase and Caplan (1986) and Kase et al. (2004) classified pontine hemorrhage into three categories: large paramedian pontine hemorrhage, unilateral basal or basotegmental pontine hemorrhage, and lateral tegmental brainstem hematoma. Among them, paramedian pontine hemorrhage is most common.

28.1.3.5.2.2.1. General clinical manifestations of pontine hemorrhage

28.1.3.5.2.2.1.1 Consciousness disturbance Cases of brainstem hemorrhage with consciousness disturbance at onset show a high mortality rate: 50–85% of the patients with severe consciousness disturbance die. However, patients with slight or no consciousness disturbance have a good prognosis.

28.1.3.5.2.2.1.2 Respiratory disturbance In brainstem hemorrhage, particularly in severe hemorrhage, several kinds of abnormal respiration can occur. Those include Cheyne–Stokes respiration, grasping respiration, apneusis, ataxic respiration, and so on. Those abnormal patterns of respiration indicate a direct or indirect effect of the hematoma on the respiratory center, and often imply a poor prognosis. In patients with respiratory abnormalities at onset, the mortality rates are more than half.

28.1.3.5.2.2.2. Clinical manifestations according to the location of pontine hemorrhage

28.1.3.5.2.2.2.1 Large paramedian pontine hemorrhage This hemorrhage occurs due to rupture of intraparenchymal paramedian branches of the basilar artery at the border zone between the tegmentum and basis pontis. It expands into surrounding areas, then extends cranially along the longitudinal axis of the brain, though not beyond the pontomedullary junction (Dinsdale, 1964). It can also rupture into the fourth ventricle.

In such severe hemorrhage, rapid development of severe consciousness disturbance occurs in almost 70–90% of the cases (Silverstein, 1972). Attacks of tonic bilateral extensor posture are common in the acute stage. Abnormal respiratory patterns, as described above, are also observed. Decerebrate posturing (Goto et al., 1980) and hyperthermia may accompany the other manifestations described above.

Neurologically, motor paralysis is usually bilateral with minor asymmetries (quadriplegia). Impairment of the corticobulbar tracts is also present. Bilateral pyramidal signs and impairment of conjugate lateral eye movements are apparent on head rotation and on ice-water irrigation of the ear. But if the hemorrhage is not so large and is asymmetrical, one-and-a-half syndrome, paralytic pontine exotropia (Sharpe et al., 1974) or non-paralytic pontine exotropia (Bogousslavsky and Regli, 1983) may develop. Pupils are commonly (but

not always) less than 1 mm in diameter, called "pinpoint pupils," but react to light in the early stage (Fisher, 1967). Of course, in the final stage the pupils may dilate and become unresponsive to light, which is one of the characteristic signs of a large brainstem hemorrhage. Ocular bobbing is another characteristic sign of large pontine hematoma. Usually, but not always, ocular bobbing develops bilaterally, which reflects severe damage to the pons with sparing of the midbrain (Fisher, 1964).

Cranial nerve palsy, such as bilateral facial palsy, and trigeminal nerve impairment are common. Sensory impairment of the four extremities and the body are also very common, but are often difficult to assess because of consciousness disturbance. The majority of massive pontine hemorrhage is fatal, but the survival period depends on the appearance of complications, such as infections, cardiac or renal dysfunction and so on.

28.1.3.5.2.2.2.2 Unilateral basal or basotegmental pontine hemorrhage It had been believed that this lesion and lateral tegmental brainstem hematoma are less common than large paramedian hemorrhage, but the presence of such rather small hematomas is now easily diagnosed by CT. A small hematoma may show a syndrome resembling those seen in lacunar infarction, such as pure motor hemiplegia (Gobernado et al., 1980) or ataxic hemiparesis (Schnapper, 1982; Kobatake and Shinohara, 1983). In cases with extension of hematoma to the tegmentum, ipsilateral VII or VI nerve palsy, or conjugate gaze palsy may be observed. A large hematoma may extend to the fourth ventricle and show a clinical course similar to that of paramedian pontine hemorrhage.

28.1.3.5.2.2.2.3 Lateral tegmental brainstem hematoma This lesion is caused by rupture of penetrating branches from the long circumferential arteries of the brainstem. Caplan and Goodwin (1982) reported: (1) conjugate gaze palsy to the ipsilateral side; (2) ipsilateral internuclear ophthalmoplegia; (3) ipsilateral miosis with preserved light reaction; (4) ataxia; (5) contralateral hemiparesis; and (6) contralateral sensory impairment were observed in lateral tegmental hemorrhage. Symptoms (1) and (2) produce one-and-a-half syndrome, with often partial disturbance of vertical eye movement, while (5) may be followed by action tremor due to impairment of the red nucleus and related fibers. Symptom (6) may be followed by pseudothalamic pain. In some cases, vertical pendular ocular oscillation and vertical oscillopsia may be observed (Lawrence and Lightfoote, 1975).

28.1.3.5.2.3. Medullary hemorrhage

Localized hypertensive medullary hemorrhage is very rare. However, there are several reports of medullary hemorrhage due to rupture of cavernous hemangioma or small AVM, which may show lateral medullary syndrome-like manifestations.

28.1.3.6. Cerebellar hemorrhage

Prompt and accurate diagnosis is essential for the appropriate management of patients with cerebellar hemorrhage. Cerebellar hemorrhage usually occurs near the dentate nucleus of the cerebellar hemisphere on one side. A detailed description of the clinical features in patients with cerebellar hemorrhage was reported by Fisher et al. (1965). However, diagnosis based on clinical manifestations alone is hazardous and confirmation by CT scan is required for a definitive diagnosis. The general clinical manifestations are as follows.

28.1.3.6.1. Clinical manifestations

28.1.3.6.1.1. Vertigo, vomiting, and headache

Generally, vertigo and headache with nausea and vomiting are prominent at the onset of cerebellar hemorrhage (Fisher et al., 1965). Vertigo and vomiting may be increased by movement. Patients often assume certain positions and do not wish to move; when such patients are moved passively, violent vomiting may occur. In patients with severe headache, differential diagnosis from SAH based on clinical manifestations alone is rather difficult.

28.1.3.6.1.2. Consciousness disturbance

Disturbance of consciousness is not commonly seen at the onset of hemorrhage, but may appear progressively over a period of 1–3 hours (Fisher, 1969; Ott et al., 1974), owing to compression of the brainstem by the hematoma and ventricular rupture of the hemorrhage. In severe cases, coma, profuse sweating on the upper half of the body or respiratory disturbance is commonly observed.

28.1.3.6.1.3. Disturbance of standing-up and gait

Gait dyspraxia and disturbance of standing-up without limb paralysis are characteristic of patients with cerebellar hemorrhage, and these are the most important points for bedside differential diagnosis of cerebellar hemorrhage from brainstem hemorrhage at the onset of hemorrhage. Patients are unable to walk because of ataxia or atonia even though there is no motor paresis.

28.1.3.6.1.4. Limb ataxia and dysarthria

In conscious patients, limb ataxia and dysarthria (slurred speech or scanning speech) are prominent. Limb ataxia is observed on the ipsilateral side. Dysarthria may be more prominent in the case of left-sided cerebellar hemorrhage.

28.1.3.6.1.5. Ocular symptoms

Paralysis of ipsilateral conjugate gaze, often with forced deviation of the eyes to the opposite side, is a reliable sign. There may be horizontal nystagmus with the rapid phase to the lesion side, and skew deviation (Freeman et al., 1973). In cases with compression of the ipsilateral pontine tegmentum by cerebellar hematoma, abducens nerve palsy, facial palsy of peripheral type, Horner's syndrome, or pinpoint pupil may be observed. Ocular bobbing has also been reported in patients with cerebellar hemorrhage (Fisher, 1964).

28.1.3.6.2. Clinical course of cerebellar hemorrhage

One of the characteristics of cerebellar hemorrhage is a sudden change of clinical course. Some patients with clear consciousness on admission can deteriorate suddenly to coma, while others recover without any functional deficit. Little et al. (1978) defined two types of cerebellar hemorrhage based upon the clinical course: one with a benign course and the other with progressive deterioration. The latter usually involves hematoma of more than 3 cm in diameter, acute obstructive hydrocephalus, and extension of hemorrhage into the fourth ventricle. Vermian hematoma, which is rare, is another variety with a poor outcome. It causes acute coma, ophthalmoplegia, respiratory disturbances, and bilateral limb weakness with extension into the pontine tegmentum and direct compression of the brainstem (Kase and Caplan, 1986). Cerebellar hemorrhage can also be a cause of neurogenic pulmonary edema (Gonçalves et al., 2005).

28.1.3.7. Caudate hemorrhage

Although Stein et al. (1984) and Kase et al. (2004) exceptionally stated that the frequency of caudate hemorrhage was more than 5% in their consecutive series of ICH, hemorrhage in the head of the caudate nucleus has rarely been reported. Characteristic findings of caudate hemorrhage are rather different from those of more common types of supratentorial ICH. Patients invariably show acute onset of vomiting, headache, stiff neck, decreased level of consciousness and behavioral change, resembling the clinical picture of SAH (Kase et al., 2004). Hemiplegia or sensory impairment, if it exists, is usually not severe, but it may accompany slight impairment of consciousness or abulia.

28.1.3.8. Intraventricular hemorrhage

If we define primary intraventricular hemorrhage as hemorrhage into the ventricles only as detected by CT or MRI, the incidence of intraventricular hemorrhage is very rare. The clinical condition of the patients ranges from minimal neurological deficits to coma or death. It also carries with it a poor prognosis of up to 80% when all four ventricles are involved (Rajendra et al., 2006).

28.2. Topics related to ICH

28.2.1. Asymptomatic microbleeds

Recent development of the gradient-echo T_2*-weighted sequence in MRI has enabled us to detect microbleeds in patients with ICH or lacunar infarction or in normative elderly subjects (Fig. 28.4) (Chan et al., 1996; Tanaka et al., 1999; Roob and Fazekas, 2000; Wong et al., 2003). It is observed in 2–6% of normative subjects (Roob et al., 2000; Takahashi et al., 2004), and is more frequent in elderly hypertensives and in subjects taking antiplatelets or anticoagulants (Takahashi et al., 2004).

The clinical importance of these microbleeds is still unclear, but microbleeds might indicate a higher risk of future intracerebral hemorrhage (Ferro, 2006; Koennecke, 2006). Therefore, more intensive treatment for hypertension and care in the use of antiplatelets or antithrombotics are necessary for these patients.

28.2.2. Asymptomatic cerebral hemorrhage

Recent clinical application of MRI has resulted in the detection of not only asymptomatic cerebral infarction, but also asymptomatic cerebral hemorrhage. For example, in our series (Shinohara et al., 1990; Nakajima et al., 1991) 179 ICH out of 2,757 patients who had undergone MRI scans during 3 years' observation were examined,

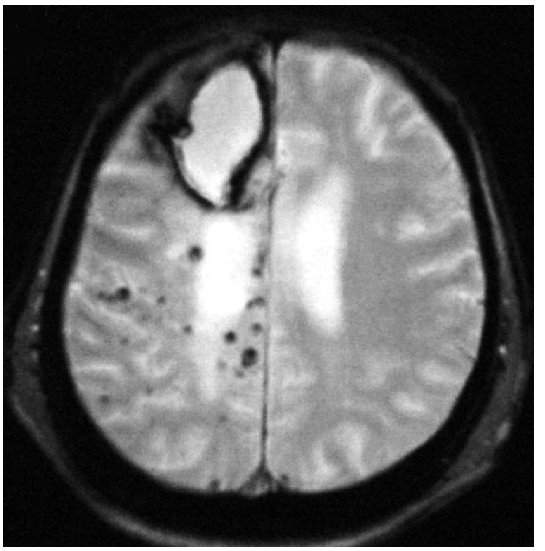

Fig. 28.4. Microbleeds observed in a 63-year-old female with right frontal lobar hemorrhage (MRI T_2* image).

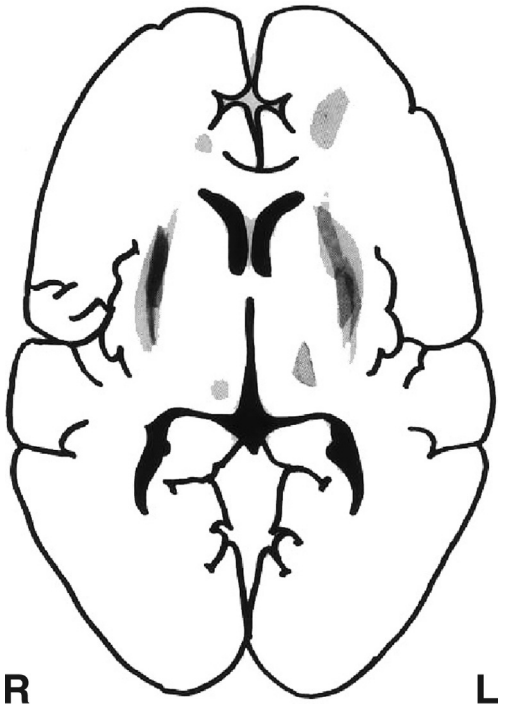

Fig. 28.5. Location of asymptomatic ICH on MRI (cumulative illustration of the sites of hematoma in 17 asymptomatic patients).

and 17 out of 179 ICH (0.6% of the subjects and 9.5% of ICH) were asymptomatic subjectively and objectively. The mean age of patients was 63 years, males were more frequent than females, and the incidence of hypertension was very high. No patients had atrial fibrillation and 5 had been receiving antiplatelets. Among the 17, 12 were diagnosed as hypertensive ICH and 5 were diagnosed as having AVM or angioma as the cause of the hemorrhage. Figure 28.5 summarizes the locations of the asymptomatic cerebral infarctions. Among these patients, 4 had a history of symptomatic ICH in another part of the brain.

As shown in Fig. 28.5, most asymptomatic ICHs are located near the external capsule, although investigators should always consider the possibility of hemorrhagic infarction in patients showing such MRI features.

28.2.3. Early spontaneous hematoma in cerebral infarction

Bogousslavsky et al. (1991) reported 15 patients in whom CT showed no bleeding within 6 hours of stroke onset, but who showed ganglionic or lobar hemorrhage less than 18 hours later, without a visible underlying infarct. They designated this picture as "early spontaneous intra-infarct hematoma." They concluded that most of these patients probably had embolism with early and extensive bleeding in the ischemic area, and they mentioned that this type of early hemorrhagic infarct may be under-recognized, while primary cerebral hemorrhage may be overdiagnosed.

28.2.4. ICH following carotid endarterectomy

Recently, carotid endarterectomy has been performed with increasing frequency. Despite the promising results of studies to assess the benefit of this technique in reducing peri-operative ischemic stroke, the incidence of ICH following carotid endarterectomy has remained much the same (0.25–1.8%) (Rockman et al., 2000).

An analysis of the literature by Russell and Gough (2004) indicated that pre-operative hypertension, recent ipsilateral non-hemorrhagic stroke, surgery for a $>90\%$ ipsilateral internal carotid artery stenosis and so on play some role in the development of ICH following carotid endarterectomy, although specific manifestations of such ICH have not been reported.

28.3. Clinical manifestations of subarachnoid hemorrhage

The subarachnoid hemorrhage (SAH) is defined as blood leakage into the subarachnoid space, either from a ruptured artery or vein or secondarily from an ICH. Estimated incidence of SAH varies from 5% to 10% of all strokes, as mentioned before. The etiology, causes, and pathophysiology are described in detail elsewhere in this book, therefore only the clinical features will be described in this chapter. Since most SAH is due to rupture of an aneurysm and ruptured aneurysm is an indication for surgical operation, early diagnosis is essential (Edner and Ronne-Engstrom, 1991). Fortunately, recent developments in neuroimaging techniques, particularly CT, enable us to detect blood in the subarachnoid space easily. Therefore, it is essential for early diagnosis of SAH to consider the clinical manifestations carefully, and to perform a CT scan as well as a lumbar puncture as early as possible.

28.3.1. Clinical manifestations of SAH

28.3.1.1. Warning signs and symptoms

SAH characteristically shows sudden onset, though some patients will experience warning signs and symptoms prior to SAH, particularly to that due to ruptured aneurysm. The frequency of such warnings varies from 27% to 60% (Okawara, 1973; King and Saba, 1974; Calvert, 1996). These warning signs and

symptoms occur more frequently in younger patients, and as regards location may occur more frequently in IC-PC aneurysm than in others (Okawara, 1973). They may be due to compression of the aneurysm, minor bleeding at the aneurysmal wall or small leakage into the subarachnoid space or vasospasm. The most frequent warning is generalized or localized headache (Locksley, 1966; Okawara, 1973), which is called "warning" or "sentinel" headache. Such headaches are often sudden, "worse than usual" and disabling, being similar to but less intense than that accompanying the major bleed (Gorelick et al., 1986). The duration between such warnings and symptomatic SAH varies from around 10 to 110 days. Other warning signs may include visual disturbance, facial pain, ocular pain, disturbance of extraocular movement, nausea, dizziness and so on (Okawara, 1973), but these are non-specific. Therefore, patients may not think that these are warning signs. The various warning signs are summarized in Table 28.2.

28.3.1.2. Clinical manifestations

Clinical manifestations of SAH include (1) sudden, severe, and unprecedented headache; (2) meningeal irritation (Kernig's sign and Brudzinski's sign, and nuchal rigidity); (3) bloody cerebrospinal fluid; (4) less marked focal neurological signs; (5) transient consciousness disturbance; and (6) preretinal hemorrhage.

28.3.1.2.1. General manifestations at onset

28.3.1.2.1.1. Headache

Headache is the most common symptom of SAH. It is often described in vivid terms such as "my head was torn open," "my head was hit with a hammer," "my head exploded," and so on. Such descriptions reflect the very acute onset of the headache, terms such as "unbearable" and "worst headache ever" being commonly used.

The duration of headache varies from 1 hour to 15 days, or rarely 3–4 weeks. Therefore, SAH should be suspected in someone with sudden severe headache that peaks within minutes and lasts more than an hour (Al-Shahi et al., 2006). Headache may be bilateral (70%) or unilateral (30%). In the case of bilateral headache, patients may complain of generalized headache (66%), and occipital (20%) and parietal (10%) headache. In the case of lateralized headache, it is usually frontal or frontoparietal. Table 28.3 (Sarner and Rose, 1967) shows the relationship between headache and neurological focal signs, and location of aneurysm. It seems difficult to judge the site of a ruptured aneurysm from the location of the headache. Pain that is felt in, around, or behind the eyes is often described in carotid–posterior communicating artery aneurysms, but may occur with middle cerebral or anterior communicating aneurysms (Toole et al., 1989). Of course, patients with consciousness disturbance or with dysphasia may not complain of headache, but usually have a headache on awakening. In cases of intracranial vertebral artery dissection and SAH, initial symptoms may be severe headache and neck pain (Blacker et al., 2004).

28.3.1.2.1.2. Consciousness disturbance

Consciousness disturbance is observed in almost half of the cases (Okawara, 1973) and is usually transient. Loss of consciousness may occur for only a few minutes or can last for days to weeks. Pakarinen (1967) reported that approximately one-third of patients show deep coma, which frequently leads to death, but this study may have included a considerable number of severe cases.

Table 28.2

Warning signs prior to rupture of intracranial aneurysm. Characteristics and interval before hemorrhage in 54 patients (Okawara, 1973)

	Site of aneurysm				
Location of headache	Anterior	Middle	Posterior	Vertebrobasilar	All sites
Occipital (%)	24	20	19	39	21
Frontal (%)	14	15	19	3	15
Temporal (%)	3	9	13	6	8
Not localized (%)	35	28	29	30	32
None (%)	24	28	20	22	24
Total number of cases	381	253	292	36	962

Table 28.3

Relationship between the location of headache and site of aneurysm (modified from Sarner and Rose, 1967)

	Carotid-ophthalmic artery	Carotid-posterior communicating art.	Carotid bifurcation	Anterior communicating artery	Anterior cerebral artery	Middle cerebral artery	Anterior in the posterior fossa	Total for each sign	% in 45 patients	% in 95 total occurrences	Average interval to major hemorrhage (days)
No. of patients	6	26	5	41	7	22	5				
Group 1											
Visual field defect		2						2	3.7	2.1	22.5
EOM impairment		6				1		7	13.0	7.4	29.6
Eye pain	1	2				1		4	8.9	4.2	53.2
Facial pain		2						2	4.4	2.1	53.2
Localized head pain		6	1	7	1	2		17	31.5	17.9	165.3
Total	1	18	1	7	1	4	0	32	71.2	33.7	110.5
Group 2											
General headache	1	6	2	7	1	7		24	44.5	25.2	10.2
Nausea		2		1	1	1		5	9.3	5.3	10.6
Neck, back pain		2	1	2		1		6	11.1	6.3	5.0
Lethargy		2	1	5				8	14.8	8.4	11.4
Photophobia		1						1	1.9	1.1	35.0
Total	1	13	4	15	2	9	0	44	97.8	46.3	10.4
Group 3											
Balance lost				1		3		4	7.4	4.2	35.7
Dizziness		1		2	1			4	7.4	4.2	13.0
Diarrhea				2		1		3	5.6	3.2	5.3
Insomnia						2		2	3.7	2.1	7.0
Feverish feeling				2				2	3.7	2.1	33.5
Motor impairment						1		1	1.9	1.1	45.5
Sensory impairment						1		1	1.9	1.1	45.5
Visual hallucination						1		1	1.9	1.1	5.0
Depression		1						1	1.9	1.1	20.0
Total	0	2	0	7	1	9	0	19	42.2	20.0	21.0
Overall total	2	33	5	29	3	22	0	95	211.1		20.9

28.3.1.2.1.3. Meningeal irritation

Blood in the subarachnoid space produces a meningeal reaction. Sarner and Rose (1967) reported that 64% of SAH showed meningeal irritation, such as nuchal rigidity and/or Kernig's sign. However, almost all patients with SAH showed some nuchal rigidity or Kernig's sign in our experience. Even if it is not clear at onset, it becomes apparent 2 or 3 days later. The intensity of the sign fluctuates depending on the site and the extent of the hemorrhage, and may persist for 2–3 weeks. Vomiting is a common feature of SAH, occurring in at least 50% of the patients.

28.3.1.2.1.4. Respiration, fever, and blood pressure and ECG changes

Respiration becomes stertorous (Binder et al., 1979) and changes in response to the elevated intracranial pressure and subsequent compression of the brainstem. Body temperature is frequently elevated to 38–39°C and usually subsides to normal within a few days. Prolonged high fever up to 39°C implies a poor prognosis. Following rupture of the aneurysm, 75–90% of patients will be hypertensive with a systolic pressure over 200 mmHg, but this may subside spontaneously over a few days.

A variety of ECG changes are found following SAH in patients who otherwise have no evidence of any pre-existing heart disease. Abnormalities attributable to SAH may be seen in 50–80% of SAH patients (Vidal et al., 1979). These changes include a spectrum of atrial and ventricular dysrhythmias, changes in the QRS complex, prolongation of QT interval, ST elevation, T wave abnormalities, prominent U wave, and so on, probably due to autonomic disturbance and, in some cases, due to secondary myocardial damage. Syndrome of inappropriate secretion of antidiuretic hormone is observed in almost 5% of the cases and we have experienced a case showing lactic acidosis (Shinohara and Yoshii, 1980).

28.3.1.2.2. Focal neurological manifestations at onset

Focal neurological manifestations depend upon several factors, such as severity of hemorrhage, increased intracranial pressure, the precise location of hemorrhage, hydrocephalus, the presence of hematoma, complicated vasospasm or cerebral infarction, and so on.

Swallowing disturbance, aphasia, homonymous hemianopsia, motor deficit, and so on, are observed with rupture of an aneurysm of the middle cerebral artery. Increased deep tendon reflexes are a particular feature of anterior cerebral artery aneurysm. Furthermore, there is a report describing paraparesis in patients with ruptured anterior cerebral artery territory aneurysms (Endo et al., 2005).

Oculomotor palsy is a characteristic of internal carotid–posterior communicating artery aneurysms (Sarner and Rose, 1967), although it may be one of the warning signs. However, the oculomotor nerve may be involved in a number of ways, including compression of the contralateral third nerve through displacement of the posterior cerebral artery, stretching and compression of the brainstem and so on.

Classically, and even now, it is said that third nerve palsies related to compressive lesions are associated with dilated pupils, ptosis, and extraocular movement disturbance, while those related to diabetes are not associated with dilated pupils. This is thought to arise from the relatively superficial position occupied by the pupil constrictor fibers and fibers to the levator palpebrae superiores within the nerve. However, Kissel et al. (1983) found that 14% of the patients with third nerve lesions due to carotid–posterior communicating artery aneurysms had normal pupils, and O'Connor et al. (1983) reported cases with papillary sparing.

Other characteristic ocular findings are so-called preretinal bleeding, which is observed within 1 hour after onset of SAH, probably due to compression of the retinal central vein. Papilledema, with an incidence of about 10% (Manschot, 1954), is caused by raised intracranial pressure.

28.3.2. Clinical findings of ruptured arteriovenous malformation

Another cause of SAH is rupture of arteriovenous malformation, which may cause ICH or SAH. Usually this will be diagnosed by CT or cerebral angiography and generally, the prognosis is better than that for rupture of an aneurysm.

28.3.3. Spinal SAH

This SAH is a hemorrhage that originates within the spinal canal. Spinal SAH is rare and accounts for less than 1% of all SAHs (Toole et al., 1989). The clinical picture is that of local pain in the spinal column. The pain may be extremely severe and worsened by movement. Spinal SAH patients characteristically show no headache and no consciousness disturbance at the onset, even if the lumbar puncture showed blood.

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Chapter 29

Eye syndromes and the neuro-ophthalmology of stroke

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Visual difficulties are common in patients with stroke. As emphasized in other chapters of this book, the clinical presentation varies depending on the type of vessel involved (arteries versus veins), the type of stroke (ischemic or hemorrhagic), the size of the arteries involved (small- versus large-artery disease) and the mechanisms of ischemia (embolic, thrombotic, or hemodynamic). Most ocular syndromes and neuro-ophthalmologic manifestations of stroke vary based on those characteristics and mechanisms.

29.1. Ischemic cerebrovascular disease

In ischemic arterial cerebrovascular disease, neuro-ophthalmic symptoms and signs mostly depend on the size and the territory of the artery involved. Cerebral venous thrombosis and venous infarction mostly produce neuro-ophthalmic symptoms and signs related to raised intracranial pressure (papilledema and visual loss) and are detailed in another chapter of this book.

29.1.1. Small-artery disease

29.1.1.1. Retinopathy and the risk of stroke and coronary artery disease

Several studies have shown that retinal microvascular changes are related to incidents of clinical stroke, stroke mortality, coronary artery disease, cerebral white matter changes detected by MRI, and cerebral atrophy (Wong et al., 2001, 2003a; Wang et al., 2003). In these studies, retinal vascular changes (generalized and focal narrowing of the retinal arterioles, arteriovenous nicking, microaneurysms) and retinopathy (cotton wool spots, retinal hemorrhages) were evaluated on fundus photographs.

The largest of these studies is the population-based Atherosclerosis Risk In Communities (ARIC) study, in which healthy, middle-aged persons with a spectrum of retinal microvascular changes detected from retinal photographs were two to three times more likely to develop an incident clinical stroke over a 3-year period (Wong et al., 2001, 2003a). This association was independent of other stroke risk factors. In addition, in persons without a history of stroke, the ARIC study further reported that these retinal microvascular changes independently correlated with poorer cognitive performance on standardized neuropsychological tests, and with the presence and severity of cerebral white matter lesions and cerebral atrophy. In the Cardiovascular Health Study, people with similar retinopathy were twice as likely to have a stroke as those without retinopathy (Wong et al., 2003b).

29.1.1.2. Arteritis

Both infectious and noninfectious inflammation affecting the central nervous system can produce visual symptoms. In some vasculitides with a predilection for large arteries, such as Takayasu's arteritis, ocular ischemia is common. Most often, vasculitides produce intraocular inflammation (uveitis) and retinal vasculitis with retinal vascular occlusions and visual loss (Biousse, 2005).

29.1.1.3. Susac's syndrome

The eponym Susac's syndrome was suggested in 1996 to describe young patients with multiple bilateral branch retinal arterial occlusions, hearing loss, and neurologic symptoms suggestive of a brain microangiopathy (Susac, 1994; Papo et al., 1998). Other terms had been previously suggested, such as RED-M (retinopathy, encephalopathy, deafness-associated microangiopathy), retinocochlear vasculopathy, and SICRET (small

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infarctions of cochlear, retinal, and encephalic tissue) (Susac, 1994; Papo et al., 1998).

Susac's syndrome usually occurs in young women but can affect men. Affected patients have multiple branch retinal occlusions that are typically bilateral, progressive hearing loss, and various neurologic presentations including psychiatric changes and encephalopathy (Table 29.1). The disease often has a chronic relapsing course punctuated by frequent remissions and exacerbations (Susac, 1994; Papo et al., 1998).

Retinal fluorescein angiography typically shows retinal arterial wall hyperfluorescence (Fig. 29.1A). The hearing loss is usually bilateral and asymmetric. It mainly involves low and medium frequencies, is usually not recognized by the encephalopathic patient, and is demonstrated by audiogram. It is believed to result from cochlear damage caused by occlusions of the cochlear end arterioles. Encephalopathy varies in severity from mild memory loss and personality changes to severe cognitive dysfunction, confusion, psychiatric disorders, seizures, and focal neurologic symptoms and signs. The brain involvement in Susac's syndrome is usually the most severe part of the disease and is frequently very debilitating.

Electroencephalograms often show diffuse slowing. Cerebrospinal fluid examination may be normal or show a variable degree of leukocytosis (lymphocytes), with elevation of protein. The neuroimaging modality of choice is the brain MRI, which typically shows multiple enhancing small lesions in both the white and gray matter (Fig. 29.1B) (Susac et al., 2003). The MRA is normal, but conventional angiography has shown evidence of vasculopathy in some patients. In a few cases, brain biopsy was performed and showed microinfarcts with some minimal perivascular lymphocytic infiltration, but no true vasculitis.

Because of the spontaneously remitting–relapsing course of Susac's syndrome, and the small number of cases reported, it is difficult to assess the efficacy of the various treatments that have been tried. Most patients have received immunosuppressive and antiplatelet/antithrombotic therapy with varied results (Susac, 1994; Papo et al., 1998).

Table 29.1

Diagnosis of Susac's syndrome

Young women >>> men
Clinical triad:
Branch retinal artery occlusions
Hearing loss
Encephalopathy
Ocular examination with retinal fluorescein angiography
Occlusion of multiple arterial branches, uni- or bilateral
Audiogram
Hearing loss, uni- or bilateral
MRI of the brain with gadolinium
Multiple small enhancing lesions in the white and gray matter

29.1.1.4. Substance abuse

Drug abusers, who intravenously inject substances synthesized for oral use may develop an obliterative

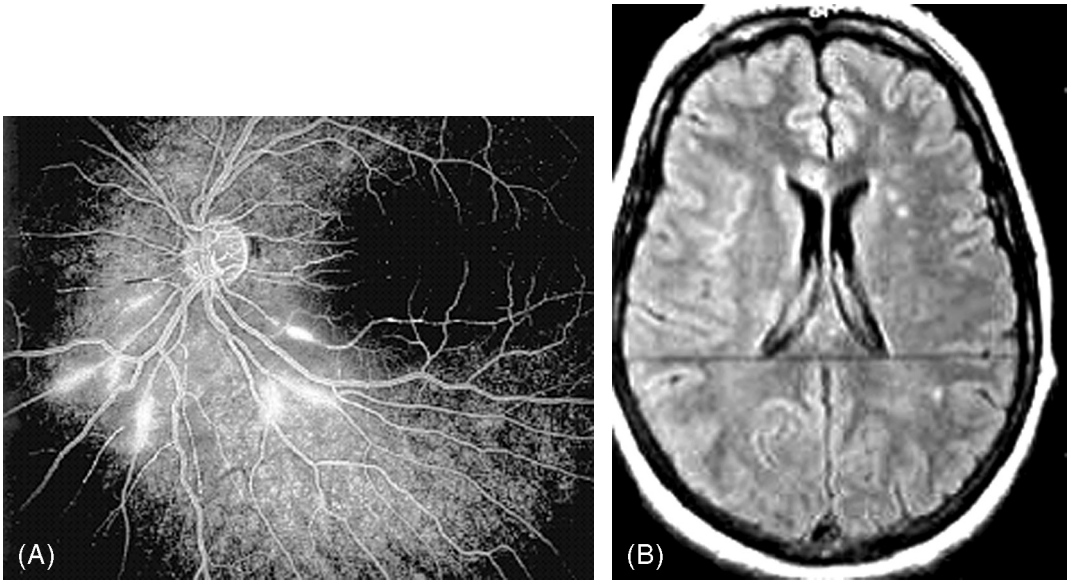

Fig. 29.1. Susac's syndrome. (A) Fluorescein angiography of the left eye of a young woman with bilateral multiple branch retinal artery occlusions related to Susac's syndrome. There are vascular occlusions associated with leakage of the fluorescein. (B) Brain MRI (FLAIR sequence) showing multiple small hypersignal.

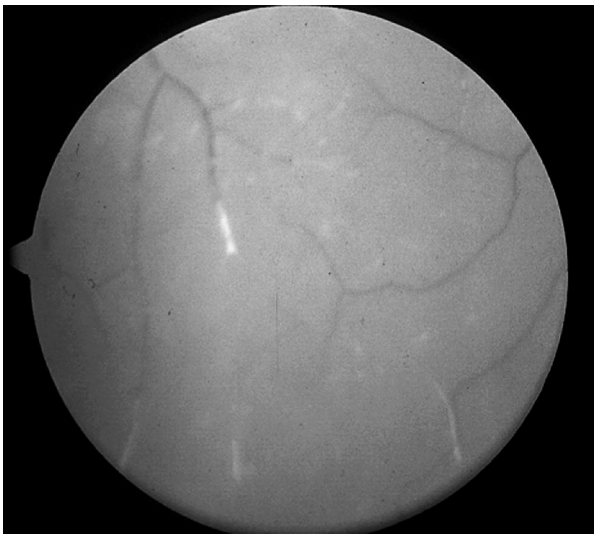

Fig. 29.2. Retinal foreign particles emboli in a patient using IV drugs.

arteritis from the effects of the fillers added to the drugs to maintain them in pill form. Common fillers include talc and microcrystalline cellulose. Pulmonary arteriovenous shunts develop and are probably the pathway by which particles reach the intracranial and intraocular arteries, producing visual loss, visual field loss, seizures, and stroke. In such patients, funduscopic examination often shows foreign particles in retinal arteries (Fig. 29.2) (Biousse, 2005).

29.1.1.5. Hereditary retinopathies

A number of rare hereditary retinopathies are associated with central nervous system abnormalities. Recent genetic characterization of three of these syndromes have shown that there is an overlap among these entities (Table 29.2) (Ophoff et al., 2001).

29.1.1.6. Hypertensive encephalopathy

Patients with systemic hypertension may develop a severe encephalopathy often associated with reversible visual loss. Hypertensive retinopathy is usually bilateral and does not always correlate with hypertensive encephalopathy. There may be associated optic nerve edema which may mimic that of raised intracranial pressure (Fig. 29.3).

29.1.1.7. Miscellaneous angiopathies of the central nervous system with ocular manifestations

A variety of other systemic disorders producing strokes may be associated with ocular abnormalities (Table 29.3). Most are inherited disorders, and are discussed in other parts of this textbook (Biousse, 2005).

29.1.1.8. Hypercoagulable states

A large number of hypercoagulable states or hematologic disorders can produce cerebral and ocular ischemia. Central retinal vein occlusion is the most common ocular vascular occlusion associated with hypercoagulable states (Fig. 29.4). Central retinal artery occlusion and ischemic optic neuropathy are very rarely associated with hypercoagulable states. Sickle cell disease may produce a specific occlusive retinal vasculopathy (Biousse, 1999).

29.1.1.9. Embolism

There are numerous causes of cerebral and ocular emboli. Ocular emboli are often visible during

Table 29.2

Characteristics of the three hereditary cerebro-ocular vasculopathies mapped to chromosome 3p21 (adapted from Biousse, 2005)

	Transmission	Ocular phenotype	Neurologic phenotype	Other
HVR	Autosomal dominant	Microangiopathy Retinal periphery and posterior pole	Multiple small lesions GM and WM Headaches	Raynaud phenomenon
CRV	Autosomal dominant	Microangiopathy Posterior pole	Cerebral pseudotumors Extensive WM lesions Dementia, headaches Death < 55 years	
HERNS	Autosomal dominant	Microangiopathy Posterior pole	Cerebral pseudotumors Extensive WM lesions Dementia, headaches Stroke Death < 55 years	Renal involvement

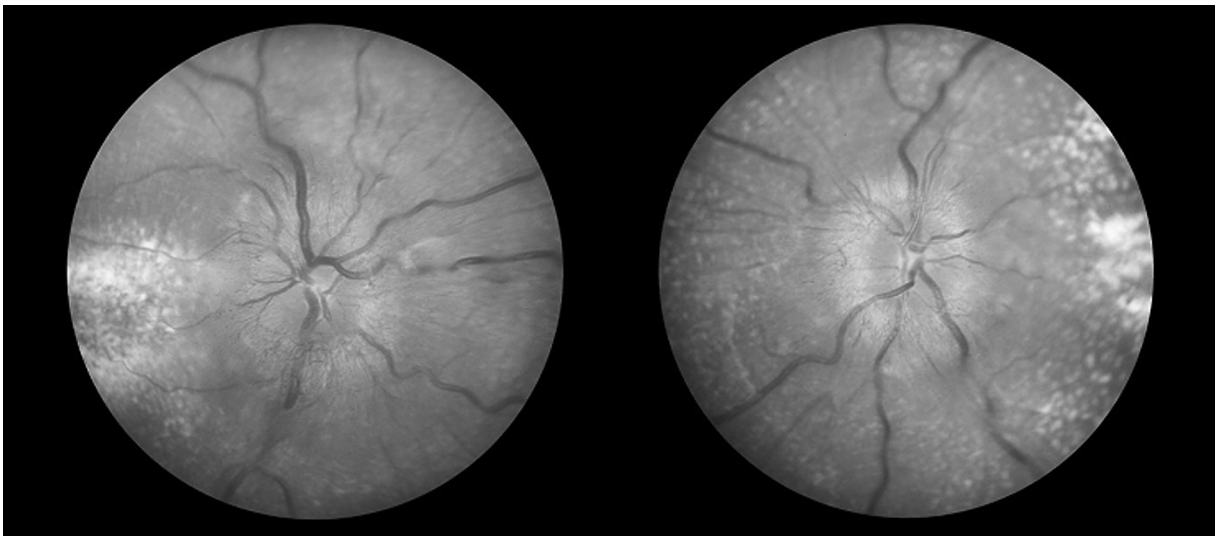

Fig. 29.3. Bilateral hypertensive retinopathy stage IV. There is optic nerve edema, the retinal arteries are attenuated, and there are retinal exudates.

Table 29.3

Miscellaneous angiopathies of the central nervous system associated with ocular manifestations (adapted from Biousse, 2005)

Disease	Mechanism of angiopathy	Transmission	Ocular manifestations
Homocysteinuria and homocysteinemia	Premature atherosclerotic occlusion of carotid arteries and large cerebral arteries	Autosomal recessive	Retinal ischemia Lens subluxation
Fabry disease (angiokeratoma corporis diffusum)	Glycosphingolipid deposit in endothelial cells, cerebral aneurysms	X-Linked recessive	Whorl-like corneal opacification. Tortuosity of vessels
Neurofibromatosis I	Arterial dissections, aneurysms, fistulae ganglioneuromas, neurofibromas	Autosomal dominant	Neurofibromas, iris Lish nodules, optic nerve gliomas, retinal hamartomas
MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, stroke-like episodes)	Proliferation of mitochondria in smooth muscle cells of cerebral vessels	Maternally inherited (point mutation in mitochondrial DNA)	Optic atrophy, chronic progressive external ophthalmoplegia, pigmentary retinopathy
von Hippel–Lindau syndrome	Cerebellar, brainstem, and spinal cord hemangioblastoma	Autosomal dominant	Retinal angiomas
Tuberous sclerosis (Bourneville disease)	Intracranial aneurysms, moyamoya syndrome	Autosomal dominant	Retinal hamartomas
Rendu–Osler–Weber syndrome (hereditary hemorrhagic telangiectasia)	Arteriovenous malformations, venous angiomas, aneurysms, meningeal telangiectasia	Autosomal dominant	Retinal telangiectasia
Ataxia-telangiectasia (Louis–Bar syndrome)	Telangiectasia	Autosomal recessive	Oculocutaneous telangiectasia
CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy)	Non atherosclerotic, nonamyloidotic angiopathy of leptomeningeal and small penetrating arteries	Autosomal dominant	Vascular retinopathy

Menkes syndrome (Kinky hair disease)	Tortuosity, elongation and occlusion of cerebral arteries	X-Linked recessive	Ocular ischemia
Marfan syndrome	Aneurysms, aortic dissection	Autosomal dominant	Lens subluxation Retinal detachment
Fibromuscular dysplasia	Arterial stenosis, arterial dissections aneurysms, carotid cavernous fistula	May be autosomal dominant. Mostly sporadic	Retinal emboli
-Ehler-Danlos syndrome (type IV)	Aneurysms, carotid cavernous fistula carotid or vertebral artery dissection	Heterogeneous	Ocular ischemia Angioid streaks
Pseudoxanthoma elasticum (Gronblad–Strandberg syndrome)	Premature atherosclerosis, aneurysms, carotid cavernous fistula	Heterogeneous	Angioid streaks, peau d'orange fundus
Moyamoya syndrome	Noninflammatory occlusive intracranial vasculopathy.	May be associated with other hereditary disorders	Morning glory disk, ocular ischemia
Sturge–Weber syndrome (encephalofacial angiomatosis)	Leptomeningeal venous angioma, arteriovenous malformations, venous and dural sinus abnormalities	Possibly autosomal dominant. Mostly sporadic	Skin, conjunctiva, episclera, uveal angiomas. Glaucoma
-Wyburn–Mason syndrome (Racemose angioma)	Cerebral arteriovenous malformations (usually brainstem)	Sporadic	Retinal arteriovenous malformations

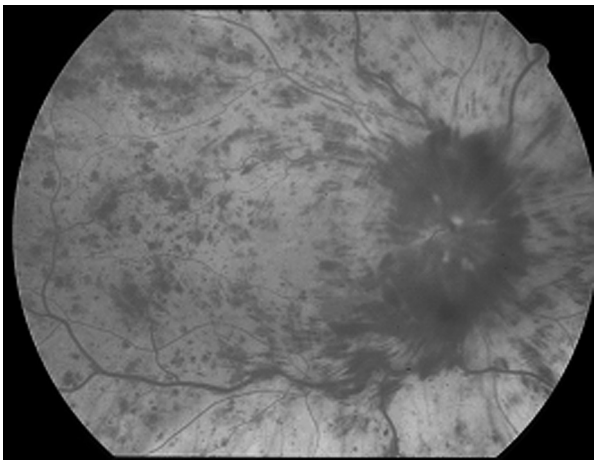

Fig. 29.4. Central retinal vein occlusion in the right eye. There are numerous retinal hemorrhages; the veins are dilated and tortuous.

funduscopic examination. The appearance of emboli may not only provide important information as to the origin of the embolic material but may also guide therapy (Table 29.4).

Retinal emboli may result in retinal ischemia and visual loss or may remain asymptomatic. Persons with retinal emboli, with or without retinal artery occlusion, seem to be at higher risk of stroke and mortality from cardiovascular disease (Wong et al., 2002; Biousse, 2005).

29.1.1.9.1. Cholesterol retinal emboli (Hollenhorst plaques)

Cholesterol emboli are yellow refractile structures that generally lodge at retinal arteriolar bifurcations where they often do not seem to obstruct blood flow (Fig. 29.5) (Pfaffenbach and Hollenhorst, 1973; Miller, 1996). The prevalence of cholesterol retinal emboli is around 1% of the general population and increases with age (Mitchell et al., 1997; Klein et al., 1999).

A wide range of cardiovascular conditions and risk factors are linked with retinal emboli, such as carotid artery plaques and stenosis, hypertension, cigarette smoking, and diabetes. A few prospective studies have documented associations between retinal emboli and stroke risk and stroke mortality (Bruno et al., 1992; O'Donnell et al., 1992; Klein et al., 1999, 2003; Babikian et al., 1991).

29.1.1.9.2. Platelet-fibrin emboli

Platelet-fibrin emboli appear as dull, gray–white plugs. Usually mobile, they adopt a long, smooth shape before breaking up in the retinal arterioles (Fig. 29.6). They are usually symptomatic and produce transient or

Table 29.4

Characteristics of retinal emboli (adapted from Biousse, 2005)

Retinal emboli	Funduscopic appearance	Source of emboli
Cholesterol (Hollenhorst plaque)	Yellow, refractile emboli. Multiple in 70% of cases. Appear wider than the arteriole. Often located at an arteriole bifurcation	Ipsilateral internal carotid artery or aortic arch atheroma
Platelet-fibrin	White, gray emboli, pale, not refractile, often multiple. Usually seen distally within the small retinal arteriole	Thrombus (carotid or aortic arch atheroma), cardiac thrombus, cardiac prosthesis
Calcium	White, large emboli, usually isolated.	Calcified cardiac valve
	Located in the proximal segment of the central retinal artery or its branches	Calcified atheromatous plaque
Talc	Multiple, yellow emboli, refractile	Intravenous drugs
Fat	Multiple whitish spots, hemorrhages, cotton wool spots	Fat emboli in the setting of leg fracture
Neoplasm	White, gray emboli, often multiples	Cardiac myxoma
Infectious	Multiple white spots (Roth's spots)	Bacterial endocarditis, candidemia

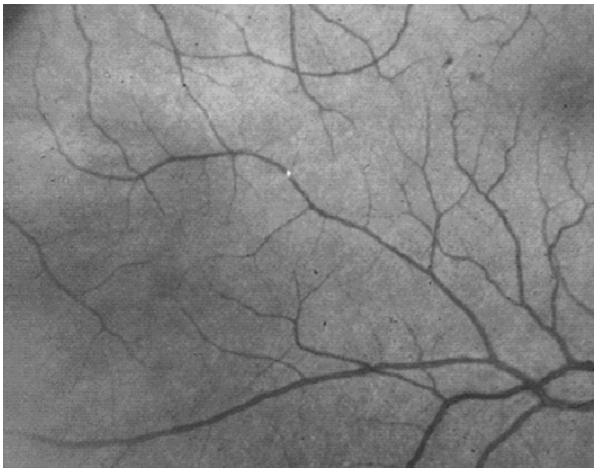

Fig. 29.5. Bright, refractile, cholesterol emboli in a retinal artery.

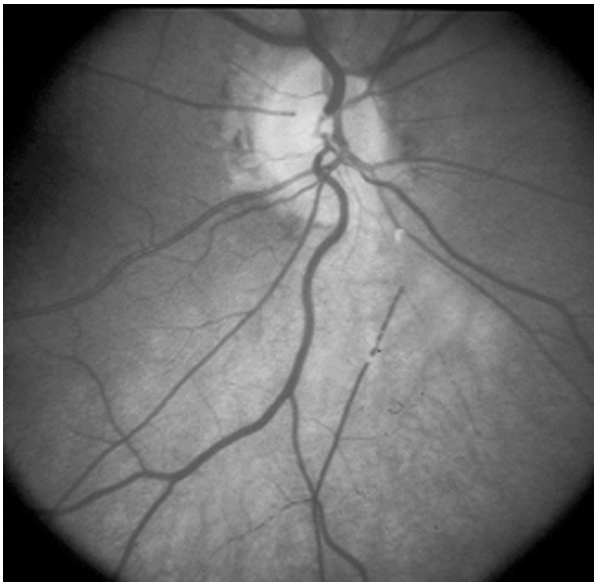

Fig. 29.6. Platelet fibrin retinal emboli responsible for localized areas of retinal ischemia.

permanent visual loss from retinal ischemia. These emboli usually arise either from the walls of atherosclerotic arteries or from the heart, particularly from its valves (Miller, 1996).

29.1.1.9.3. Calcium emboli

Emboli composed of calcium may lodge in the retinal and cerebral arteries of patients with rheumatic heart disease, calcific aortic stenosis, calcification of the mitral valve annulus, and other disorders of the heart and great vessels that predispose to formation of calcium. Unlike cholesterol emboli and platelet-thrombin emboli, which tend to pass through the retinal circulation or resolve over time, calcific emboli tend to lodge permanently in retinal vessels, occasionally resulting in the development of collateral vessels forming shunts around the embolic blockage (Miller, 1996).

29.1.1.9.4. Tumor emboli

Carcinoma, sarcoma, lymphoproliferative tumors, and atrial myxoma are all capable of spreading via the circulation. The appearance of tumor emboli in retinal vessels is nonspecific and is often described as white, gray or "cream-cheese-like" material (Miller, 1996).

29.1.1.9.5. Fat emboli

Systemic intravascular dissemination of neutral fat globules is most often a complication of trauma to the long bones. Nontraumatic fat embolism occurs in clinical settings other than severe trauma, such as acute pancreatitis, alcoholic fatty liver disease, and contusion of fatty viscera during surgery. Fat emboli may occur in retinal vessels, with a funduscopic appearance of multiple white emboli located at various points along the vessels (Miller, 1996).

29.1.1.9.6. Septic emboli

Septic emboli occur most often in patients with subacute and acute bacterial endocarditis. Septic emboli appear as gray–white plugs in one or more retinal arteries, sometimes surrounded by a localized intraretinal hemorrhage. The appearance is thus that of a "Roth spot"—a focal hemorrhage with a white or gray center. Such lesions develop when septic emboli cause disruption of the vessel wall, resulting in hemorrhage with a central area of organisms and white blood cells. The lesions may heal without spreading to other areas, or they may extend into the vitreous to produce a suppurative endophthalmitis (Miller, 1996).

29.1.1.9.7. Air embolism

Air embolism occasionally occurs when air is injected into an organ or tissue of the body, after chest injuries, and during pulmonary, cardiac, or neurologic surgery. In some of these cases, the emboli reach the retinal vessels and produce severe visual loss that usually recovers over several hours to days (Biousse, 2005).

29.1.1.9.8. Foreign body embolism

Any foreign material that is allowed access to the arterial (and occasionally the venous) circulation has the potential to cause embolic cerebral or ocular strokes (Biousse, 2005).

29.1.1.10. Acute decreased cerebral and ocular perfusion

The visual pathways are particularly vulnerable to any decrease in their blood or oxygen supply. The effects of decreased cerebral perfusion on visual function vary mostly depending on the collateral circulation. Medial occipital regions are often affected, resulting in bilateral symmetric visual loss ("cerebral blindness"). Visual loss may also result from unilateral or bilateral infarction of the retina or optic nerve. The severity of visual loss ranges from mild or transient blurred vision in one eye to irreversible total blindness in both eyes.

The appearance of the ocular fundus in patients who lose vision from blood loss and hypotension is variable. In some cases, there is mild to severe optic disk swelling, and the pupillary responses to light are sluggish or absent, indicating severe damage to the optic nerve. In other cases, the fundi appear normal. When normal fundi are associated with intact pupillary responses to light in patients who are blind or nearly so, a post-geniculate location of infarction (usually the occipital lobes) is certain. When the fundi appear normal and there are sluggish or absent pupillary responses to light, retrobulbar but pregeniculate infarction has occurred (so-called posterior ischemic optic neuropathy); optic atrophy eventually develops about 4–6 weeks after the infarction.

Patients who undergo open-heart surgery with cardiopulmonary bypass may develop severe hypotension during the procedure, as might patients who undergo other types of cardiac and noncardiac surgery. Such patients may develop transient or permanent visual difficulties from damage to various parts of the visual sensory and ocular motor systems. Although damage to the optic radiations or occipital cortex may be the most common cause of visual disability in these patients, hypotensive ischemic retinopathy and optic neuropathy may also cause visual loss. Extended back surgery in the prone position has been mostly associated with posterior ischemic optic neuropathies (Ho et al., 2005).

29.1.2. Large-artery disease

Anterior and posterior large-artery circulation ischemia is often associated with visual symptoms and signs which may precede a cerebral infarction.

29.1.2.1. Anterior circulation (carotid artery disease)

A variety of transient and permanent visual symptoms and signs may develop in patients with disease in the carotid arterial system. The hallmark of most of these disturbances is their monocular nature. However, homonymous and bitemporal visual field defects and bilateral simultaneous visual loss may result from diseased carotid arteries and their branches, particularly when the disease is bilateral.

29.1.2.1.1. Transient monocular visual loss ("amaurosis fugax")

This is the most common and perhaps most important ophthalmologic symptom of disease of the internal carotid arterial system. The term "amaurosis fugax" is often used to describe any cause of transient monocular visual loss and should be abandoned (Fisher, 1989). As indicated in Table 29.5, there are numerous nonvascular causes of transient monocular visual loss (Biousse, 2005).

Table 29.5

Differential diagnosis of transient monocular visual loss (TMVL)

Vascular ("amaurosis fugax")
Orbital ischemia (ophthalmic artery)
Retinal ischemia (central retinal artery and its branches)
Optic nerve ischemia (short posterior ciliary arteries)
Choroidal ischemic (posterior ciliary arteries)
Retinal migraine (vasospastic amaurosis fugax)
Central retinal vein occlusion
Ocular diseases
Anterior segment:
Dry eyes
Keratoconus
Hyphema
Angle closure glaucoma
Retinal detachment
Central serous retinopathy
Optic nerve disorders
Papilledema (transient visual obscurations)
Optic disk drusen (transient visual obscurations)
Congenitally anomalous optic disk (transient visual obscurations)
Optic nerve compression (gaze-evoked TMVL)
Uhthoff's phenomenon

Patients with this symptom complain of acute, monocular loss of vision that may be partial or complete. Some episodes of transient monocular visual loss are accompanied by a sensation of color or by photopsias consisting of showers of stationary flecks of light that disappear quickly. Such "positive" visual phenomena are rare, and are more suggestive of a hemodynamic mechanism. They seem to be particularly frequent in carotid artery dissections.

Most episodes of transient monocular visual loss last 2–30 minutes and then resolve spontaneously, usually over seconds to minutes. Rare patients experience transient monocular visual loss lasting several hours. In the NASCET, the duration of the episodes of transient monocular visual loss ranged from 15 seconds to 23 hours, with a median duration of 4 minutes and only 8% lasting more than 1 hour (Streifler et al., 1995; Benavente et al., 2001).

Some patients experience only one episode of transient visual loss, but most have more than one. Episodes may occur at extremely variable intervals. Multiple episodes of transient visual loss in the elderly should raise the possibility of giant cell arteritis. In some patients, transient monocular visual loss occurs when the patient is exposed to bright light. Light-induced transient visual loss is caused by the inability of borderline ocular circulation to sustain the increased retinal metabolic activity associated with exposure to bright light. Delay in the regeneration of visual pigments in the photoreceptor layer of the retina following exposure to bright light results in consequent blurred or absent vision that persists until regeneration of pigments is achieved. These patients usually have severe carotid artery disease that compromises flow to the orbital and ocular vessels. Similarly, post-prandial transient visual loss results from a temporary retinal and choroidal hypoperfusion occurring when blood flow already compromised by severe carotid artery disease is diverted to the gut following a meal—a mesenteric steal phenomenon (Furlan et al., 1979; Ross Russell and Page, 1983; Wiebers et al., 1989; Levin and Mootha, 1997).

Patients examined in the midst of an attack of transient, monocular visual loss may have spasmodic closure of the entire central retinal arterial tree (Winterkorn et al., 1993). In other cases, stationary or mobile emboli may be seen in the retinal arteries of the affected eye (Miller, 1996). Transient monocular loss of vision usually occurs as an isolated phenomenon, unassociated with other neurologic symptoms or signs. In particular, neither headache nor eye pain are common during an attack. Nevertheless, some patients, particularly young adults, experience headache at the time of visual loss. Painful transient monocular visual loss should raise the possibility of giant cell arteritis in the elderly and angle closure glaucoma or carotid dissection in the younger adult (Table 29.6).

Six vascular risk factors have recently been associated with a higher risk of ipsilateral stroke in patients with transient monocular visual loss and stenosis of at least 50% of the diameter of the internal carotid artery (Table 29.7) (Benavente et al., 2001). There is evidence to suggest that only patients with at least three of these risk factors should be considered for a carotid endarterectomy (Benavente et al., 2001). The evaluation and management of patients with vascular transient visual loss are detailed in another chapter of this textbook.

Table 29.6

Differential diagnosis of painful transient monocular visual loss

Giant cell arteritis
Internal carotid artery dissection
Ocular ischemic syndrome
Angle closure glaucoma
Retinal migraine*

*Retinal migraine is a diagnosis of exclusion.

Table 29.7

Predictors of the 3-year risk of ipsilateral stroke among 174 medically treated patients with transient monocular visual loss and stenosis of at least 50% of the diameter of the internal carotid artery. Adapted from Benavente et al. (2001)

Risk factor	Risk with factor present	Risk with factor absent	Relative risk
Age at least 75 years	32.5	11.2	2.9 (0.9–10.6)
Male sex	15.3	6.8	2.2 (0.8–7.0)
History of hemispheric TIA or stroke	22.7	10.0	2.3 (1.0–6.1)
History of intermittent claudication	22.5	10.4	2.2 (0.8–5.6)
Ipsilateral stenosis of 8–94% internal carotid artery	21.1	9.8	2.2 (0.9–5.5)
No collaterals on angiography	14.8	6.2	2.4 (0.7–8.3)

CI = confidence interval.

29.1.2.1.2. Permanent visual loss

Partial or complete monocular loss of vision may occur in patients with carotid artery disease, usually in the ipsilateral eye. This results most often from a central retinal artery occlusion (CRAO) or from one or more branch retinal artery occlusions (BRAO). In such cases, an embolus may or may not be seen in affected vessels. Other causes of monocular visual loss in patients with carotid artery disease include venous stasis retinopathy, the ocular ischemic syndrome, and rarely, ischemic optic neuropathy (Table 29.8) (Biousse, 2005).

The second major visual sign of carotid occlusive disease is a partial or complete contralateral homonymous visual field defect. This is most often caused by occlusion of branches of the middle cerebral artery, but it may result from occlusion of the anterior choroidal artery or some of its branches to the optic tract and lateral geniculate body. A few patients with carotid occlusive disease have severe visual deficits caused by a combination of monocular visual loss from ocular circulation insufficiency and contralateral homonymous field loss from damage to the ipsilateral post-chiasmal visual sensory pathway.

29.1.2.1.3. Central and branch retinal artery occlusion

Patients who experience a retinal stroke usually complain of acute loss of visual acuity, visual field, or both. Permanent visual loss may be preceded by episodes of transient monocular visual loss, but occurs most often without warning symptoms. Patients with a central retinal artery occlusion almost always have extremely poor visual acuity in the affected eye.

Ophthalmoscopic findings in a patient with a central retinal artery occlusion depend on the extent of the occlusion and the duration between the event and the examination. Acute central retinal artery occlusion is characterized by diffuse pale swelling of the retina, a macular "cherry red" spot, and attenuation of the retinal vessels (Fig. 29.7) (Ros et al., 1989; Connolly et al., 2000). Within 2–3 weeks at most, the retinal

Table 29.8

Ocular manifestations of carotid disease

Asymptomatic retinal emboli
Transient monocular visual loss
Central retinal artery occlusion
Ophthalmic artery occlusion
Episcleral artery dilation
Venous stasis retinopathy
Ocular ischemic syndrome
Ischemic optic neuropathy*
Optic nerve compression*
Horner's syndrome
Ocular motor nerve paresis
Referred pain

*Carotid disease is only very rarely responsible for these events.

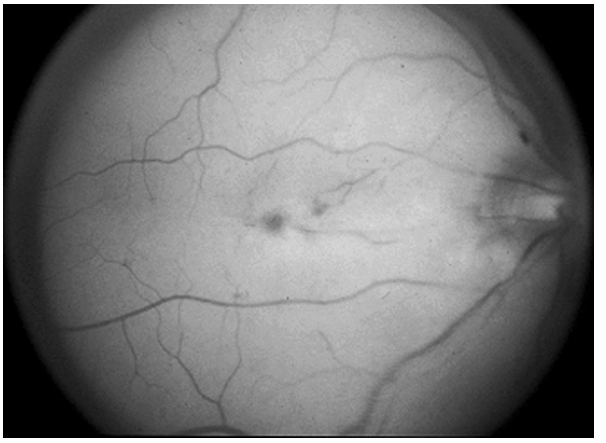

Fig. 29.7. Central retinal artery occlusion. The retina is whitish and the arteries are very attenuated. There is a cherry red spot.

vessels, although remaining extremely narrow, again appear to contain a continuous column of blood. Occasionally, the size of the retinal arterioles becomes almost normal; however, the optic disk usually remains pale. When there is a patent cilioretinal artery, the territory supplied by the vessel remains normal and is surrounded by edematous retina. Emboli are seen in about 11–40% of central retinal artery occlusions and in 60–70% of branch artery occlusions (Ros et al., 1989; Connolly et al., 2000). The most common emboli that occlude retinal arterioles are cholesterol plaques, fibrin-platelet plugs, and calcium fragments (Table 29.4).

Carotid artery disease is responsible for the majority of retinal infarctions. In patients with embolic retinal stroke who have no evidence of disease in the carotid arterial system, the aortic arch or the heart are the most likely sources of emboli. In most cases, the emboli are of the platelet-fibrin or calcific type; in others, they are tumor emboli, usually from cardiac myxoma (Fig. 29.8).

There is no definitive treatment of a central retinal artery occlusion. Both medical and surgical approaches are disappointing. Conventional therapy for a central retinal artery occlusion includes ocular massage, anterior chamber paracentesis, topical medications to lower the intraocular pressure, intravenous or oral acetazolamide, and inhalation of a mixture of 95% oxygen and 5% carbon dioxide (carbogen), aspirin, isovolemic hemodilution, oral vasodilators, topical beta-blockers, heparin and warfarin, but these treatments do not seem to improve the outcome of central retinal artery occlusions (Rumelt et al., 1999). Selective intra-arterial thrombolysis (infusion directly in the ophthalmic artery) with urokinase or tissue plasminogen activator (tPA) has been suggested by some authors (Mueller et al., 2003; Rumelt and Brown, 2003). However, anecdotal success must be weighed against the risk for major side-effects. While awaiting the results of an ongoing prospective randomized trial evaluating intra-arterial tPA in the treatment of acute central retinal artery occlusion, treatment should be decided on a case-by-case basis.

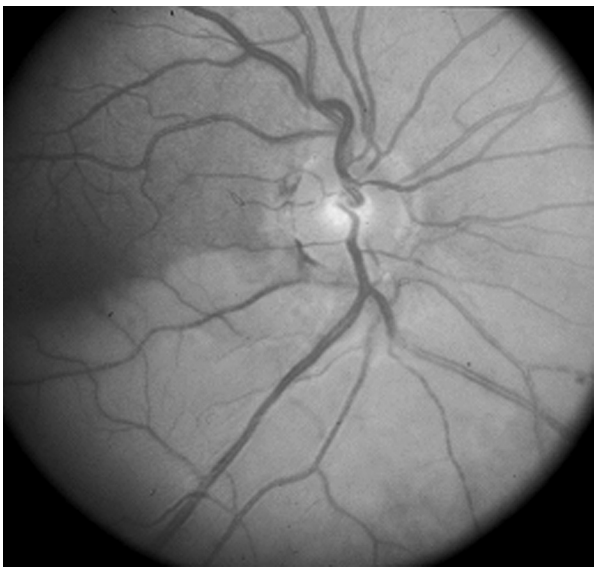

Fig. 29.8. Inferior branch retinal artery occlusion in a patient with mitral valve stenosis. The ischemic retina is whitish.

29.1.2.1.4. Ophthalmic artery occlusion

Ophthalmic artery occlusion usually results from large emboli in the trunk of the ophthalmic artery. The visual loss is profound and the prognosis poor. Funduscopic examination shows white edematous retina with poor or no retinal artery filling, and disk edema. Since the choroidal circulation is also compromised, there is no "cherry red" spot.

29.1.2.1.5. Ischemic optic neuropathy

Both anterior ischemic optic neuropathy and posterior ischemic optic neuropathy may rarely occur in patients with carotid artery disease and may even be the initial manifestation of internal carotid artery occlusion. This is extremely rare, and in most cases the optic neuropathy is not specifically related to the internal carotid artery disease but rather is a sign of widespread atherosclerosis affecting both large and small vessels. Alternatively, it may reflect shared vascular risk factors (Hayreh et al., 1994).

29.1.2.1.6. Homonymous visual field defects

In patients with ischemia in the carotid territory, homonymous visual field defects may occur with lesions of the optic tract, lateral geniculate body, and anterior radiations. Damage to the optic tract produces a contralateral homonymous hemianopia associated with a relative afferent pupillary defect on the side of the hemianopia (contralateral to the side of the lesion), and (4–6 weeks later) bilateral retinal nerve fiber layer and optic nerve atrophy. Because of its dual blood supply, lesions of the lateral geniculate body may produce a homonymous, quadruple sectoranopia. Lesions of the anterior optic radiation may produce a contralateral homonymous hemianopia, usually in association with other neurologic symptoms or signs (Biousse, 2005).

29.1.2.1.7. Venous stasis retinopathy and ocular ischemic syndrome

Venous stasis retinopathy—also called hypotensive retinopathy—is associated with severe carotid obstructive disease and poor collateral circulation. The retinopathy

is characterized by insidious onset, diminution or absence of venous pulsations, dilated and tortuous retinal veins, peripheral microaneurysms, and dot-blot hemorrhages in the midperipheral retina. Patients with this condition complain primarily of generalized blurred vision in the affected eye or may be asymptomatic. Symptoms of carotid insufficiency, such as transient monocular loss of vision, decreased vision after exposure to bright light (see above), and, in particular, orbital pain are common. Venous stasis retinopathy may occur as part of the ocular ischemic syndrome or in isolation. It is found in up to 20–30% of patients with carotid occlusive disease (Russell and Page, 1983; Klijn et al., 2002). Venous stasis retinopathy usually resolves spontaneously if arterial patency can be restored (Klijn et al., 2002). In many cases, however, there is persistent visual dysfunction from irreversible retinal ischemic changes. If ocular perfusion cannot be improved, the affected eye may develop neovascularization of the iris and optic disk as well as other signs of ocular ischemia. In such cases, panretinal photocoagulation may prevent progression of the condition and may actually produce regression of neovascularization (Biousse, 2005).

The ocular ischemic syndrome (also called ischemic ocular inflammation or chronic ocular ischemia) is a progressive disorder that results from hypoperfusion of the eye. Patients describe blurred or dull vision that may be transient or persistent. Visual loss is typically insidious and slowly progressive. Some patients describe positive after-images on exposure to bright light. The early findings in chronic ocular ischemia suggest intraocular inflammation. The affected eye is often red, with a diffuse episcleral vascular injection, rather than a ciliary flush as would be expected in inflammatory disease (Fig. 29.9) (Mitzener et al., 1997). The ocular fundus shows mild to severe venous stasis retinopathy with possible neovascularization. The appearance thus may mimic diabetic retinopathy. Some patients with the ocular ischemic syndrome have severe ocular or peri-orbital pain. In eyes with persistent hypoperfusion, neovascularization of the iris (rubeosis iridis), retina, optic disk, and anterior chamber angle develop. Other signs of ocular ischemia include corneal edema, uveitis, cataract formation, and a mid-dilated and poorly reactive pupil. The prognosis for vision in eyes affected by untreated chronic ischemia is extremely poor. Although early retinopathy may resolve spontaneously with the development of collateral circulation, significant loss of vision is almost always irreversible once tissue infarction occurs.

The treatment of the ocular ischemic syndrome is aimed at preservation and improvement in visual function and treatment of the underlying process

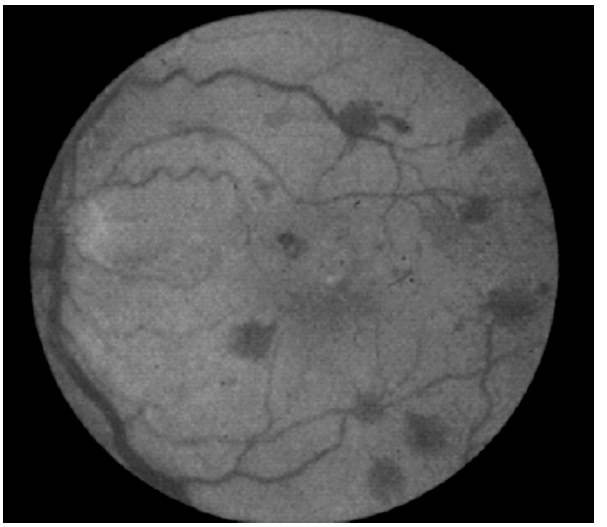

Fig. 29.9. Venous stasis retinopathy in a patient with severe carotid occlusive disease. The veins are dilated and there are dot-blot hemorrhages in the mid-periphery of the retina.

(Mitzener et al., 1997). The first requires a relative decrease in the oxygen requirements of the eye, thus reducing the drive for neovascularization. This is usually accomplished by ablation of retinal tissue by laser panretinal photocoagulation or peripheral retinal cryotherapy. When severe carotid artery stenosis is the underlying condition, endarterectomy may be used to re-establish flow. When, as is usually the case, the artery is occluded, a superficial temporal artery to middle cerebral artery bypass procedure may be beneficial if the external carotid artery is patent. When the internal and external carotid arteries are occluded, some form of revascularization of the external carotid artery may be of some benefit. However, all the procedures of revascularization have been associated with ocular complications such as retinal or vitreal hemorrhages and elevated intraocular pressure. Moreover, patients with such severe carotid disease and poor collateral circulation often have a high surgical risk. No therapy is clearly effective in reversing the ocular ischemic syndrome.

29.1.2.1.8. Horner's syndrome

Although it is more common in carotid artery dissections, Horner's syndrome may occur in patients with atherosclerotic carotid artery disease (Fig. 29.10) (Biousse et al., 1998). Most such patients have complete occlusion of the internal carotid artery, and the Horner's syndrome is associated with other neurological symptoms and signs of carotid artery disease. Horner's syndrome occurring in patients with occlusion of the internal carotid artery is almost always postganglionic (third order).

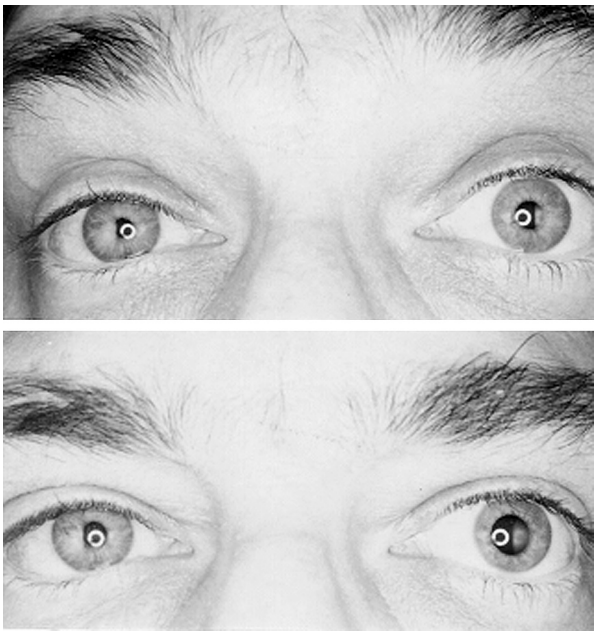

Fig. 29.10. Right Horner's syndrome in a patient with a spontaneous right internal carotid dissection. The right pupil is slightly smaller than the left in the light (top) and the amount of anisocoria increases in the dark (bottom). There is mild reduction of the palpebral fissure on the right.

29.1.2.1.9. Ocular motor nerve paresis

Rarely, patients with acute occlusion or severe stenosis of the internal carotid artery may experience one or more ocular motor nerve pareses on the side of the occlusion, either in isolation or with signs of ocular ischemia (Schievink et al., 1993). In some cases of isolated oculomotor nerve palsy, ischemia of the nerve probably results from reduction of blood flow through mesencephalic branches of the anterior choroidal artery. In other cases, blood supply to the cranial nerves themselves, which originates from branches of the internal carotid artery, may be compromised (Lapresle and Lasjaunias, 1986; Biousse, 2005).

29.1.2.1.10. Referred pain

Isolated ocular pain may be a symptom of carotid occlusive disease, even without other symptoms and signs of vascular disease. It is usually a referred pain resulting from ischemia or compression of the trigeminal branches. It may also be part of the ocular ischemic syndrome (Biousse, 2005).

29.1.3. Posterior circulation

The vertebrobasilar system supports the neural components of the entire brainstem ocular motor mechanism as well as those of the posterior visual sensory pathways and visual cortex. For this reason, ocular motor and visual symptoms and signs play a major role in the diagnosis of vascular insufficiency in the vertebrobasilar system (see Tables 29.9–29.14).

Table 29.9

Causes of cerebral visual loss

Vascular:
Vertebrobasilar ischemia (posterior cerebral artery territory)
Cerebral anoxia
Cerebral venous thrombosis (superior sagittal sinus)
Hypertensive encephalopathy
Eclampsia
Head trauma
Occipital mass (tumor, abscess, vascular, hemorrhage)
Demyelinating disease
Infection:
Occipital abscess
Meningitis
PML
Creutzfeld–Jacob disease
Toxic:
Cyclosporine
Tacrolismus
Mercury poisoning
Metabolic:
Hypoglycemia
Porphyria
Hepatic encephalopathy
Migraine (visual aura)
Occipital lobe seizures

29.1.3.1. Visual loss

29.1.3.1.1. Transient binocular visual loss

Episodes of transient visual loss are very common in vertebrobasilar ischemia. Episodes of blurred, dim, or complete loss of vision occur in patients with vertebrobasilar insufficiency almost as often as attacks of vertigo. The visual loss is always bilateral, with both eyes being affected simultaneously and symmetrically (Hoyt, 1959; Caplan, 2000; Devuyst et al., 2002; Biousse, 2005). The change in vision may be described as a sudden "grayout of vision," "a sensation of looking through fog or smoke," or "the feeling that someone has turned down the lights." Most attacks of blurred vision that result from vertebrobasilar insufficiency last less than a minute. Attacks of longer duration may be accompanied by flickering, flashing "stars" of silvery light in a homonymous or altitudinal field of vision. They may occur alone or in combination with other transient symptoms in the vertebrobasilar territory. The episodes of blurred vision that occur in patients with occipital ischemia must be differentiated from other causes of transient or permanent visual loss (Table 29.9). Transient, complete

Table 29.10

Ocular movement in midbrain infarctions

Upper midbrain syndrome
Vertical gaze palsy
Upgaze
Downgaze
Combined upgaze and downgaze
Dorsal midbrain syndrome
Slowness of smooth pursuit movements
Torsional nystagmus
Pseudoabducens palsy
Divergence-retraction nystagmus
Lid retraction
Skew deviation (alternating)
See-saw nystagmus
Monocular elevation palsy
Crossed vertical gaze paresis
Vertical one-and-a-half syndrome
Middle midbrain syndrome
Nuclear third nerve palsy
Fascicular third nerve palsy
isolated
with contralateral hemiparesis (Weber's syndrome)
with ipsi- or contralateral hemiataxia (Claude–Nothnagel's syndrome)
with contralateral abnormal movements (Benedikt's syndrome)
Lower midbrain syndrome
Internuclear ophthalmoplegia
isolated
with fourth nerve palsy, ataxia and nystagmus
Superior oblique myokimia

Table 29.11

Ocular movement disorders in pontine infarctions

Paramedian syndrome:
Ipsilateral gaze paralysis
Complete gaze paralysis
Loss of ipsilateral horizontal saccades
Loss of both horizontal and vertical saccades
Downbeat nystagmus
Tonic conjugate ocular deviation away from lesion
Unilateral internuclear ophthalmoplegia
Bilateral internuclear ophthalmoplegia (WEBINO syndrome)
Internuclear ophthalmoplegia and skew deviation
One-and-half syndrome
Paralytic pontine exotropia
Ocular bobbing
Lateral pontine syndrome:
Horizontal gaze palsy
Horizontal and rotatory nystagmus
Skew deviation
Internuclear ophthalmoplegia
One-and-half syndrome
Ocular bobbing

Table 29.12

Ocular movement abnormalities in medullary infarctions

Lateral medullary syndrome:
Nystagmus in primary position
Positional nystagmus
Skew deviation
Ocular tilt reaction
Floor on ceiling phenomenon
Saccadic lateropulsion
Ocular lateropulsion
Medial medullary syndrome:
Upbeat nystagmus
Horizontal gaze plasy
Vertical gaze palsy

90–180° inversion of the visual image occasionally occurs.

29.1.3.1.2. Homonymous hemianopic defects

An isolated homonymous visual field defect of sudden onset is the hallmark of a vascular lesion in the occipital lobe. Such a lesion is usually the result of infarction in the territory supplied by the posterior cerebral artery. The field defect may be complete or incomplete, but when it is incomplete or scotomatous, it is usually extremely congruous (Fig. 29.10). When there is a complete homonymous hemianopia, macular sparing is common, and the occipital pole is usually spared. Patients with a homonymous visual field defect caused by ischemia in the territory of the posterior cerebral artery have normal visual acuity. When both occipital lobes are infarcted, visual acuity is usually severely impaired but the amount of visual loss is symmetric in both eyes. In some cases of occipital lobe infarction, the anterior portion of the lobe is unaffected, resulting in sparing of part or all of the peripheral 30° of the contralateral, monocular temporal field—the temporal crescent. Symptoms of posterior cerebral artery occlusion usually occur without warning. The patient may have a slight sensation of dizziness or light-headedness and then becomes aware of a homonymous visual field defect. Some patients initially experience complete blindness, with vision returning in the ipsilateral homonymous visual field within minutes. Pain in the ipsilateral eye or over the ipsilateral brow (contralateral to the hemianopia) is an important although inconstant symptom in such patients (Knox and Cogan, 1962). This pain is referred from the tentorial branches of the trigeminal nerve.

Table 29.13

Ocular movement abnormalities in cerebellar infarctions

Saccadic dysmetria
Square wave jerks
Increased slow drift
Impaired smooth pursuit with the head moving
Nystagmus:
Gaze-evoked nystagmus
Rebound nystagmus
Downbeat nystagmus
Positional nystagmus
Ocular flutter
Skew deviation
Impaired optokinetic nystagmus
Increased gain of the vestibulo-ocular reflex

29.1.3.2. Disorders of higher cortical function

A number of syndromes described by patients as "difficulty seeing" or "difficulty reading" may result from occipital ischemia (Biousse, 2005). Alexia without agraphia results from infarction of the left occipital lobe and disruption of the left ventral visual association cortex and its outflow tracts to the left angular gyrus, thus interrupting input from the right occipital area to the language verbal association area. Patients can usually name individual letters or numbers, but they cannot read words or phrases. Although they are able to write a letter, they cannot read it back moments later. Patients in whom there is infarction of the left occipital lobe and the splenium of the corpus callosum have no visual information to send to the language

Table 29.14

A few named ocular motor syndromes to remember. Adapted from Biousse (2005)

Syndrome	Clinical syndrome	Anatomic correlation
Weber	Ipsilateral CN III	***Ventral medial mesencephalic:***
	Contralateral hemiplegia affecting the face, arm, and leg	CN III fascicle Ipsilateral corticospinal tract
Claude-Nothnagel	IL CN III	***Intermediolateral mesencephalic:***
	Contralateral ataxia	CN III Cerebellar peduncle
Benedikt	Ipsilateral CN III	***Paramedian mesencephalic:***
	Contralateral tremor	CN III fascicle
	Contralateral ataxia	Ipsilateral red nucleus
Raymond	Ipsilateral CN VI	***Ventromedial pons:***
	Contralateral hemiparesis (often affects the face)	Abducens nerve fascicle Corticobulbar and corticospinal tracts
Millard Gubler	(Raymond's syndrome + ipsilateral peripheral CN VII)	
	Ipsilateral CN VI	***Ventromedial pons:***
	Contralateral hemiparesis (often affects the face)	CN VI fascicle CN VII fascicle
	Ipsilateral peripheral VII	Corticobulbar and corticospinal tracts
Foville	Ipsilateral peripheral CN VII	***Lateral inferior pontine:***
	Ipsilateral deafness	CN VII fascicle or nucleus
	Ataxia	Auditory nerve or cochlear nucleus
	Ipsilateral facial hypoesthesia	Middle cerebellar peduncle and cerebellar hemisphere
	Contralateral pain and thermal hypoesthesia	Descending tract and nucleus of ipsilateral CN V Spinothalamic tract
Wallenberg	Ipsilateral CN IX, X	***Lateral medullary***
	Ipsilateral facial hypoesthesia	CN IX and X
	First order Horner	Descending tract and nucleus of ipsilateral CN V
	Contralateral loss of pain and temperature in trunk and extremities	Sympathetic pathway Lateral spinothalamic tracts
	Ipsilateral cerebellar syndrome	Fibers to the inferior cerebellar peduncle
	Ocular dysmetria, nystagmus, skew deviation, ocular tilt reaction	
	Vertigo, lateropulsion	

center from the left occipital lobe, and information from the right occipital lobe cannot be transmitted via the corpus callosum.

Gerstmann syndrome results from infarction of the left angular gyrus secondary to an occlusion of the left posterior cerebral artery. Patients have difficulty in telling right from left, difficulty in naming digits on the patient's own or another's hand, constructional dyspraxia, agraphia, and difficulty calculating.

Associative visual agnosia is present in some patients with a left posterior cerebral artery occlusion. It consists of difficulty understanding the nature and use of objects presented visually. However, they can trace with fingers, and they can copy an object presented in the hand and explored by touch or verbally described by the examiner.

Prosopagnosia results from occlusion of the right posterior cerebral artery. Patients with this condition have difficulty recognizing familiar faces. The patients may also have difficulty revisualizing to themselves what a given object or person should look like, and their dreams are often devoid of visual imagery.

Visual neglect is much more common after occlusion of the right posterior cerebral artery with infarction of the right parietal lobe than it is after occlusion of the left posterior cerebral artery.

The syndrome of cortical blindness occurs with bilateral posterior cerebral artery occlusions. Patients with this syndrome may have premonitory episodes of bilateral visual blurring or focal brainstem ischemia before they develop acute, bilateral, simultaneous visual loss caused by bilateral simultaneous homonymous hemianopia. Many cases of cortical blindness are caused by basilar artery thrombosis. The pupils and fundus examination are normal. Many of the patients experience photopsias or formed visual hallucinations while they are totally blind. Denial of blindness or Anton's syndrome is common. Bilateral occipital lobe infarction can produce decreased central visual acuity in both eyes without any obvious hemianopic defect. The loss of central vision probably results from generalized ischemia of the occipital lobes and is symmetric in both eyes, unless there is an associated unilateral or asymmetric ocular disease.

Bálint's syndrome can occur in patients who experience bilateral simultaneous or sequential posterior cerebral artery occlusions. Patients with this syndrome present with a triad of "psychic paralysis of visual fixation," "optic ataxia," and visuospatial disorientation. Patients with Bálint's syndrome have a variety of abnormalities of fixation and tracking. They have great difficulty locating a stationary object in space, although they can maintain fixation on the object once they locate it. They can track a moving target, but if the target begins to move rapidly, it is lost and cannot be relocated. Bálint's syndrome probably occurs much more frequently after bilateral watershed infarctions of the parieto-occipital regions from systemic hypotension than from thrombo-embolic carotid or vertebrobasilar disease.

Simultagnosia may develop in patients with bilateral superior occipital lobe strokes. Such patients complain of piecemeal perception of the visual environment wherein objects may look fragmented or even appear to vanish from direct view. Simultagnosia is caused by a defect in visual attention that results in an inability to sustain visuospatial processing across simultaneous elements in an array. Simultagnosia, like Bálint's syndrome and other higher disorders of visual processing and attention, occurs much more frequently after systemic hypotensive crises than from occlusion of the posterior cerebral arteries. Common causes include cardiac arrest and intraoperative hypotension.

Achromatopsia occurs in association with prosopagnosia when occipital lobe infarction is limited to the lower banks of the calcarine fissures on both sides,

29.1.3.3. Visual hallucinations

Formed visual hallucinations may be produced by vertebrobasilar ischemia. These hallucinations, which may last 30 minutes or more, may be associated with decreased consciousness, but they usually occur in an otherwise alert patient who is aware that the visual images are not real. The hallucinations are generally restricted to a hemianopic field, and they are often complex. Some of the visual hallucinations that occur in patients with posterior cerebral artery occlusion are palinoptic, with the hallucinations consisting of recently or previously seen images (Biousse, 2005).

29.1.3.4. Diplopia

Transient binocular horizontal or vertical diplopia is a common manifestation of vertebrobasilar ischemia. The diplopia may result from transient ischemia of the ocular motor nerves or their nuclei (ocular motor nerve paresis) or from transient ischemia to supranuclear or internuclear ocular motor pathways (skew deviation, internuclear ophthalmoplegia, gaze paresis). In most cases, the diplopia is not isolated and the patient has other neurologic symptoms suggesting vertebrobasilar ischemia (Hommel and Bogousslavsky, 1991; Bogousslavsky et al., 1994; Vuillemier et al., 1995; Bassetti et al., 1996; Amarenco, 1991; Moncayo and Bogousslavsky, 2003).

Persistent disturbances of eye movements are extremely common in patients with vertebrobasilar ischemia. Ocular motor nerve paresis, internuclear

ophthalmoplegia, supranuclear deficits and nystagmus develop based on the anatomical location of the lesion (Tables 29.9–29.13). Nystagmus produces oscillopsia which is often described by the patients as "jumping of the eyes" or "jumping of vision."

29.2. Hemorrhagic cerebrovascular disease

Primary and secondary intracerebral hemorrhages may produce visual field defects and abnormal eye movements. The type of neuro-ophthalmic signs depends mostly on the anatomical location of the lesion. In addition, raised intracranial pressure often results in chronic papilledema and subsequent visual loss (Qureshi et al., 2001). Similarly, subarachnoid hemorrhage often results in papilledema and visual loss as a result of raised intracranial pressure.

Terson syndrome describes retinal, subhyaloid, and vitreal hemorrhage that occurs in the setting of subarachnoid hemorrhage. The presumed mechanism is that of acute raised intracranial pressure with sudden elevation of ocular central venous pressure. The diagnosis is often delayed as patients often have altered mental status and are not aware of the visual loss. Unless there is an associated retinal detachment, treatment is usually deferred and a vitrectomy is performed only if the hemorrhage does not resolve spontaneously (Biousse, 2005).

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Chapter 30

Post-stroke seizures

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30.1. Introduction

It was Hippocrates who first described epilepsy as a "sacred disease" of the brain due to natural causes that was often associated with hemiplegia. However, it was not until the 1800s that Hughlings Jackson, and then Gowers, documented stroke as a cause of epilepsy (Taylor et al., 1931). It is now clear that stroke is an important cause of seizures and epilepsy, particularly in older age groups. Data indicates that persons over the age of 65 years comprise over 15% of the population and the highest age-specific incidence of epilepsy is in elderly persons. Stroke accounts for 30% of newly diagnosed seizures in patients over 60 years old (Forsgren, 1990) and is the most commonly identified etiology of secondary epilepsy (11%) (Hauser et al., 1990).

There have been many epidemiological studies conducted on seizures and epilepsy after stroke, often with differing results. This relates to heterogeneous study design, differences in terminology and definitions, study setting (hospital versus community), variable periods of follow-up, small sample sizes, and inconsistencies in seizure identification and classification. This chapter will provide an overview of the various epidemiological studies covering both ischemic and hemorrhagic stroke and attempt to give an understanding of the limited knowledge of the pathogenesis of post-stroke seizures and their outcome and management.

30.2. Timing and frequency of post-stroke seizures

Reports on the frequency of seizures following stroke vary quite widely because of differing stroke patient populations, sample sizes studied, follow-up periods, definitions used for stroke and seizures, use of investigations such as neuroimaging (CT/MRI) and type of statistical analysis. In most studies the follow-up period was less than a few weeks, so documentation of late onset seizures, or recurrent seizures (epilepsy), is limited. Table 30.1 summarizes those studies of early and late onset post-stroke seizures where patients with pre-stroke seizures were excluded, and CT was used in the diagnosis of cerebral ischemia or hemorrhage.

Overall, seizures generally occur in about 10% of patients with stroke. The largest prospective hospital-based study is the Seizures After Stroke Study (SASS), which examined the frequency and outcome of seizures in 1,897 consecutive stroke patients (Bladin et al., 2000). In this study eligible patients were followed for a mean of 9 months with an overall frequency of seizures of 9%. Seizures were significantly more common after intracerebral hemorrhage (10.6%) compared to cerebral infarction (8.6%). Similar rates of seizures have been seen in community-based studies. In the Oxfordshire Community Stroke Project, the cumulative actuarial risk of having a seizure after ischemic stroke was 4.2% at 1 year and 9.7% at 5 years (Burn et al., 1997).

Early onset seizures are usually defined as those occurring within 2 weeks of stroke although some studies have used definitions such as those first occurring within 24–48 hours, 1 week, 2 weeks, or 1 month. They are reported in anywhere from 2% to 5% of patients with recent stroke, more commonly after intracerebral hemorrhage than infarction. The frequency of early seizures in ischemic stroke ranges from 2% to 33%, with the majority (50–78%) occurring within the first 24 hours of stroke (Camilo and Goldstein, 2004). The frequency of late post-ischemic

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Table 30.1

Frequency of seizures after stroke

	Setting	Seizures ischemic stroke %/ hemorragic stroke %	Early seizures	Late seizures	Epilepsy
Lamy et al. (2003)	Hospital	5.8%	1 week; 2.4%	> 1 week; 3.4%	2%
Arboix et al. (2003)	Hospital	2.2%	48 hours; 2.2%	—	—
Labovitz et al. (2001)	Community	3.1%	1 week; 3.1%	—	—
Bladin et al. (2000)	Hospital		2 weeks; 4.8%	> 2 weeks; 3.8%	2%
Reith et al. (1997)	Hospital/ community	3/8	14; 4	—	—
Burn et al. (1997)	Community		24 hours; 2%	> 24 hours; 3%	3%
Arboix et al. (1997)	Hospital	2/4	48; 2	—	—
Giroud et al. (1994)	Hospital/ community	5/15	15 days; 5	—	—
Lanceman et al. (1993)	Hospital	7/25	30 days; 3.8%	> 30 days; 3.2%	—
Kotila and Waltimo (1992)	Rehabilitation unit	14/15	3	14%	—
Davalos et al. (1992)	Hospital	4/8	48; 5	—	—
Kilpatrick et al. (1990)	Hospital	—	2 weeks; 6.5%	—	—
Sung and Chu (1989)	Hospital	– /5%			
Faught et al. (1989)	Hospital	–/25%	17%	8%	—
Gupta et al. (1988)	Hospital	—	2 weeks; 33%	> 2 weeks; 67%	2 weeks; 39%
Berger et al. (1988)	Hospital	—	17%	—	7%

stroke seizures in recent hospital studies varies little at 3–4%. When intracerebral hemorrhage alone has been studied, seizures have been reported in 5–25% of patients.

The frequency of recurrent, otherwise unprovoked seizures (epilepsy) after stroke has rarely been quantified because of limited patient follow-up in most studies and may also be confounded by the use (or lack of use) of anticonvulsant drugs (Camilo and Goldstein, 2004). Indeed, one retrospective study found that 86% of patients having recurrent seizures were either not taking their seizure medications or had subtherapeutic blood levels (Gupta et al., 1988; Camilo and Goldstein, 2004). The overall rate of post-stroke epilepsy is approximately 2–4%. In ischemic stroke, early seizures can be an independent risk factor for the subsequent development of late and recurrent seizures (epilepsy) (Lamy et al., 2003; Camilo and Goldstein, 2004). In the SASS there was seizure recurrence in 55% (34 of 62) of patients with late post-ischemic seizures and multivariate analysis indicated that late-onset seizures were a significant independent risk factor for epilepsy (hazard ratio [HR]: 12.37) (Bladin et al., 2000). This is similar to that observed in other studies with longer follow-up periods (Burn et al., 1997) and higher than that reported for the general population experiencing a first unprovoked seizure (Hauser et al., 1998; Camilo and Goldstein, 2004).

30.3. Types of seizure

Details of seizure subtype in studies of post-stroke seizures are limited by the retrospective design of the majority of the studies and are potentially confounded by interviewer and recall bias related to obtaining seizure descriptions from patients or observers. Reports indicate that up to 63% of seizures may not be recognized by patients (Blum, 1996). Partial seizures predominate after cerebral infarction and hemorrhage (Faught et al., 1989; Sung and Chu, 1989, 1990; Kilpatrick et al., 1990; Giroud et al., 1994; Lo et al., 1994; Bladin et al., 1998). In contrast, one study has reported a higher frequency (50%) of generalized tonic-clonic seizures without focal onset in patients with early-onset seizures (Arboix et al., 2003).

Approximately 50–90% of early-onset seizures appear to be simple partial seizures usually simple motor in type, sometimes secondarily generalizing (Kilpatrick et al., 1990; Giroud et al., 1994; Bladin et al., 2000; Lamy et al., 2003). Tonic–clonic seizures are also common but it is probable that in many cases the focal onset is unwitnessed or overlooked. Complex

partial seizures occur relatively rarely after stroke but are likely under-represented in these studies, as only 15% of those with partial seizures are aware of their spells (Blum, 1996).

Status epilepticus has been reported from 0.14% to 13% of stroke patients with seizures depending on stroke type (Kilpatrick et al., 1990; Sung and Chu, 1990; Lo et al., 1994; Bladin et al., 2000; Rumbach et al., 2000; Velioglu et al., 2001). Status epilepticus can be a presenting feature of cerebral infarction or hemorrhage. Seizure activity is often focal motor involving the hemiparetic limbs or may be tonic–clonic in nature (Berger et al., 1988; Faught et al., 1989; Sung and Chu, 1989; Kilpatrick et al., 1990). Lobar hemorrhages are more commonly associated with status epilepticus than other types of intracerebral hemorrhage (Sung and Chu, 1989).

In the SASS, although the incidence of early seizures was common, status epilepsy developed in only 3% of the stroke population overall with no significant difference between ischemic and hemorrhagic stroke (Bladin et al., 2000). This compares with a 0.9% rate from a population-based study (Labovitz et al., 2001). Alternatively, because stroke is a relatively common condition, it accounted for up to 25% of cases of status epilepticus in some series (Asfar et al., 2003).

Cerebrovascular disease is a common cause of status epilepticus in older patients. In addition the mortality of status epilepticus increases with advancing age beyond 60 years and duration of seizures (DeLorenzo et al., 1992), hence the importance of early treatment. Important causes of status epilepticus after stroke are anticonvulsant withdrawal and noncompliance (Lowenstein et al., 1993).

30.4. Risk factors for post-stroke seizures

30.4.1. Stroke location and size

The most consistent risk factor for seizures at the onset or following cerebral infarction or hemorrhage is cortical involvement, according to pathological (Richardson and Dodge, 1954) and clinical studies (Olsen et al., 1987; Berger et al., 1988; Faught et al., 1989; Kilpatrick et al., 1990; Davalos et al., 1992; Lanceman et al., 1993; Giroud et al., 1994; Lo et al., 1994; Arboix et al., 1997; Burn et al., 1997; Kraus and Berlit, 1998; Bladin et al., 2000; Rumbach et al., 2000; Lamy et al., 2003). Larger strokes and the carotid arterial territory in the anterior hemispheres carry a higher risk of seizures (Lo et al., 1994; So, 1996; Burn et al., 1997) especially in the context of cerebral infarction (Davalos et al., 1992; Lanceman et al., 1993; Arboix et al., 1997; Bladin et al., 2000).

In the SASS (Bladin et al., 2000), cortical infarcts carried a two-fold (HR: 2; CI: 1.2–3.7) increase in producing seizures and were typically in the fronto-parietal lobe in the region of the motor strip and extending down to the insula. Cortical hemorrhage had a three-fold increase in risk of seizures (HR: 3; CI: 1.4–7.4).

With respect to intracerebral hemorrhage, lobar hemorrhages carry a higher risk of seizures compared to those located subcortically. However, patients with small lobar hemorrhages, because of their cortical location, experience seizures more often than patients with larger bleeds located elsewhere (Berger et al., 1988; Faught et al., 1989; Weisberg et al., 1991; Bladin et al., 1996). Other factors such as intracranial shift or presence of blood in the CSF spaces did not influence the occurrence of seizures in hemorrhagic stroke (Berger et al., 1988; Bladin et al., 2000).

Subcortical infarction is less commonly associated with seizures than cortical infarcts. Seizures have been noted in up to 3% of patients following lacunar infarcts (Kilpatrick et al., 1990; Giroud et al., 1994; Arboix et al., 1997; Bladin et al., 2000) and in 23% of patients with striatocapsular infarction (Giroud and Dumas, 1995), although CT scanning was normal in the majority of these patients, and brain MRI was often not performed. It is possible that CT underestimates the number of patients with cortical ischemia in subcortical stroke and therefore the possibility of cortical involvement cannot be completely excluded.

Results of EEG and functional neuroimaging studies seem to support the concept that seizures in the setting of apparent lacunar stroke may be a reflection of concurrent cortical involvement. Early studies found abnormal EEGs in up to 38% of patients with lacunar infarction (Macdonell et al., 1988). A population-based study also found lateralized EEG abnormalities in the subgroup of lacunar stroke patients with early seizures (Giroud et al., 1994). Consistent with this observation, a small study using quantitative EEG analysis also reported lateralized abnormalities in 83% of patients with lacunar infarctions (Kapelle et al., 1990; Camilo and Goldstein, 2004). A more sensitive indicator may be single photon emission tomography (SPECT), positron emission tomography (PET), or magnetic resonance imaging (MRI) (Olsen et al., 1986; Perani et al., 1987; Reith et al., 1997). The small subgroup of patients with lacunar infarcts in SASS showed evidence of cortical dysfunction on single photon emission CT and had lateralized EEG abnormalities even when the routine CT scan was normal (Bladin et al., 2000). One neurochemical explanation for seizures occurring is the possible release of glutamate from axonal terminals

arising from injured thalamocortical neuronal projections (Ross and Ebner, 1990).

30.4.2. Stroke type

The greater risk of seizures following intracerebral hemorrhage compared to infarction has been noted. Seizure risk does not appear to increase with amount of ventricular or cisternal blood nor the presence of hydrocephalus or shift of intracranial structures (Berger et al., 1988; Bladin et al., 1996). Likewise, hemorrhagic infarction did not confer a higher risk of seizures in the SAS study (Bladin et al., 1998).

Results of early clinical and autopsy studies suggested that seizures are more common with cardio-embolic infarction than other types of ischemic stroke (Richardson and Dodge, 1954; Mohr et al., 1978; Giroud et al., 1994; Kraus and Berlit, 1998). This association has not been demonstrated in other studies (Black et al., 1983; Kilpatrick et al., 1990; Kittner et al., 1990; Davalos et al., 1992; Bladin et al., 1998). In the Seizures After Stroke Study (SASS) patients who had a probable cardio-embolic stroke were not at elevated risk of a first seizure or recurrent seizures (Bladin et al., 2000).

In the Lausanne Stroke Registry (Bogousslavsky et al., 1988) none of the 137 patients with presumed embolism had seizures. Similarly, there was no association between seizure at onset and the presence of a cardiac source of embolism in the National Institute of Neurological Disorders and Stroke (NINDS) Stroke Data Bank study (Kittner et al., 1990). Therefore, clinical data showing a clear relationship between cardiogenic embolism and seizures are lacking.

The greater risk of seizures following intracerebral hemorrhage compared to infarction has been noted. Seizure risk does not appear to increase with amount of ventricular or cisternal blood nor the presence of hydrocephalus or shift of intracranial structures (Berger et al., 1988; Bladin et al., 1996). Likewise, hemorrhagic infarction did not confer a higher risk of seizures in the SAS study (Bladin et al., 1998).

Less than 2% of patients with transient ischemic attacks experience seizures (Kilpatrick et al., 1990; Giroud et al., 1994). However, distinguishing a TIA from a focal seizure can sometimes be difficult. This is particularly true in cases of so-called limb-shaking TIAs. Limb-shaking TIAs are thought to result from focal cerebral hypoperfusion due to carotid artery occlusive disease (Baquis et al., 1985; Tatemichi et al., 1990; Zaidat et al., 1999; Klempen et al., 2002).

30.4.3. Clinical features

Reported clinical predictors for seizures after ischemic stroke are stroke severity, acute agitated confusional state, altered consciousness, and persisting paresis (Olsen et al., 1986; Arboix et al., 1997; Reith et al., 1997) (Table 30.2). In the SASS patient age, sex,

Table 30.2

Independent predictors of early seizures, late seizures, and epilepsy after stroke.

	Independent predictors*		
	Early seizures	Late seizures	Epilepsy
Kammersgard and Olsen (2005)	—	—	Younger age, stroke severity, ICH, lesion size, early seizures
Lamy et al. (2003)	Cortical location, stroke severity	Large infarct, cortical signs, early seizures	Late seizures
Labovitz et al. (2001)	Lobar location	—	—
Bladin et al. (2000)	Cortical location, stroke severity	Late seizures	
Reith et al. (1997)	Stroke severity	—	—
Arboix et al. (1997)	Cortical location confusional state	—	—
Burn et al. (1997)	Cortical location	NS	NS
So (1996)	Hemispheric infarction	Early seizures, stroke recurrence	Early seizures, stroke recurrence
Lo et al. (1994)	Cortical location	—	—
Giroud et al. (1994)	Loss of consciousness, males	—	—

*Independent predictors based on multivariable analysis.
Adapted from Camilo and Goldstein, 2004.

hemisphere affected, and vascular risk factors did not influence seizures following stroke (Bladin et al., 1996). In the SASS and Copenhagen stroke studies, stroke severity conveyed a six-fold to ten-fold increase in seizures risk in patients with ischemic stroke but not hemorrhagic stroke. However, a subsequent study found that after adjusting for stroke location and subtype, stroke severity was no longer associated with early seizures after ischemic stroke (Labovits et al., 2001). Stroke extent, as measured by CT scan, was not independently associated with the development of seizures in the SASS (Bladin et al., 2000). Therefore, the independent affect of stroke severity, as measured either clinically or based on radiographic studies, remains uncertain.

30.5. Risk factors for post-stroke epilepsy

The issue of epilepsy following stroke has been poorly studied, mainly because of lack of long-term patient follow-up. Most patients suffering seizures within the first few weeks of a stroke do not have recurrent seizures, but have a higher risk than the age-matched population. Those with late onset seizures are possibly at higher risk (up to three-fold) for epilepsy than those with early-onset seizures (Louis and McDowell, 1967; Lesser et al., 1985; Faught et al., 1989; Sung and Chu, 1989, 1990; Hornig et al., 1990; Weisberg et al., 1991). Cortical lesions increase the risk of epilepsy after cerebral infarction or hemorrhage (Olsen et al., 1987). With respect to intracerebral hemorrhage, lobar hemorrhage (Sung and Chu, 1989) and an identified structural cause (Weisberg et al., 1991) increase the risk of epilepsy.

30.6. Pathogenesis

Little is known about the mechanism of seizures associated with stroke but it appears clear that cortical involvement is important in both infarction and hemorrhage. Because of the different frequency of seizures associated with cerebral hemorrhage compared to infarction, seizure pathogenesis is likely to be different. The temporal occurrence of post-stroke seizures, clinical features, and proposed pathogenesis share similarities with brain trauma associated seizures (Jennett, 1979; Willmore, 1993).

Because most patients who experience early seizures after cerebral infarction or hemorrhage do not suffer recurrences, the pathogenesis of the two phenomena is likely to be different (Lesser et al., 1985). In patients with cerebral infarction, early-onset seizures are thought to result from transient cellular neurochemical dysfunction leading to electrically irritable tissue (Heiss et al., 1992; Luhmann, 1996). Acute ischemia causes increased extracellular concentrations of glutamate, an excitatory neurotransmitter that may result in secondary neuronal injury, particularly in the ischemic penumbra (Heiss et al., 1992; Buchkremer-Ratzmann et al., 1998; Camilo and Goldstein, 2004). Recurrent epileptiform neuronal discharges can occur in neural networks of surviving neurons exposed to glutamate (Sun et al., 2001) and transient peri-infarct depolarizations have been observed in the penumbra after experimental occlusion of the middle cerebral artery (Branston et al., 1977; Iijima et al., 1992; Camilo and Goldstein, 2004). Other metabolic events at the time of stroke may also have an impact. For example, it has been demonstrated in experimental models that hyperglycemia (Uchino et al., 1996) and aberrations of sodium and calcium biochemistry at the time of ischemia enhance epileptogenesis. The size of the ischemic penumbra may also be influential. There is a correlation between the number and the total duration of depolarizing events and infarct (and penumbra) volume in the setting of ischemia (Back et al., 1996; Camilo and Goldstein, 2004). A study using CT and SPECT technology detected a three-fold greater blood flow defect in stroke patients with seizures compared to those without, which is possibly indicative of a larger, more electrically irritable ischemic penumbra (Bladin et al., 1996).

As acute metabolic derangements are reversed, seizures are less likely. In contrast to early-onset seizures, late-onset seizures and epilepsy are thought to be caused by structural changes such as gliosis and the development of meningocerebral scar tissue (Jennett, 1979). Changes in membrane properties, deafferentation, selective neuronal loss, and collateral sprouting may result in hyperexcitability and neuronal synchrony sufficient to cause seizures (Luhmann et al., 1955; Stroemer et al., 1995). Pronounced neocortical neuronal hyperexcitability was found in primary somatosensory neurons of rats 10–17 months after transient forebrain ischemia (Smith et al., 1984; Mudrick, 1988; Luhmann et al., 1955; Camilo and Goldstein, 2004).

Similar issues may be relevant to the occurrence of seizures after intracerebral hemorrhage compounded by the presence of red blood cells and iron, known neurotoxic agents. Some authors have raised the possibility that extravasated red cells and particularly the iron they contain may be responsible for the development over time of a chronic epileptic focus (Chusid and Kopeloff, 1962; Willmore et al., 1978; Lesser et al., 1985).

30.7. Seizures and stroke outcome

Whether or not seizures per se worsen the outcome of ischemic stroke is uncertain. Some authors have noted higher in-hospital mortality for patients with early seizures following cerebral infarction or hemorrhage (Shinton, 1988; Arboix et al., 1997; Vernino et al., 2003) but not others (Black et al., 1983; Davalos, 1992; Kilpatrick et al., 1990; Reith et al., 1997). Nonetheless, after accounting for stroke severity, population-based studies have not found an association between early seizures and mortality (Reith et al., 1997; Labovitz et al., 2001). In contrast, the SASS investigators found higher mortality rates in patients with seizures after ischemic stroke (but not hemorrhagic stroke) at 30 days and 1 year (Bladin et al., 2000). Those with seizures also had a significantly poorer neurological score during the acute hospitalization and worse Rankin scores at follow-up (median 9 months).

In the SASS, seizures were identified as an independent risk factor for death following cerebral infarction but not cerebral hemorrhage (Bladin et al., 1998). Predictors of a poor prognosis after stroke are the size of the lesion, initial stroke severity, and a reduced level of consciousness (Davalos et al., 1992; Reith et al., 1997). There has been a reported lower mortality and better functional outcome for lobar compared to deeper hemorrhages because of their superficial nature (Kase et al., 1982).

Exacerbation of pre-existing neurological deficits post-seizure can last more than a week or several months (Bogousslavsky et al., 1992; Hankey, 1993). A large prospective observational study with a 1-year follow-up found no effect of late seizures on rehabilitation outcome (Paolucci et al., 1997; Camilo and Goldstein, 2004). Although epilepsy significantly affects health-related quality of life (Leidy et al., 1999), the additional impact of post-ischemic seizures on post-stroke quality of life has not been firmly established (Camilo and Goldstein, 2004). It is plausible that early seizures in penumbral areas might be harmful because of the additional metabolic stress they may cause in already vulnerable tissue (Reith et al., 1997). Such an exacerbation is more likely after a prolonged seizure and a longer partial seizure before generalization, indicating the importance of prompt seizure control.

In some studies the occurrence of status epilepticus in stroke carries a high mortality (Rumbach et al., 2000) while in others no independent relationship between the occurrence of status epilepticus and mortality rate can be inferred (Velioglu, 2001). However, the numbers of patients with generalized as compared with partial-status epilepticus are small and often not specifically analyzed. In contrast, a prospective study reported an almost three-fold increase in mortality among patients with acute ischemic stroke and generalized convulsive status epilepticus as compared with patients with acute ischemic stroke alone (39% versus 14%, $p < 0.001$) (Waterhouse et al., 1998; Camilo and Goldstein, 2004).

30.8. Role of the EEG

EEG changes after stroke are not specific, but when present tend to be focal (Gupta et al., 1988; Faught et al., 1989; Lo et al., 1994; Arboix et al., 1997). With cerebral ischemia most commonly there is slowing, loss of normal background activity, and reduction in overall amplitude (Faught, 1993). Other findings include periodic lateralizing epileptiform discharges (PLEDS), sharp activity and frontal intermittent delta activity (FIRDA). These changes can resolve within months of cerebral infarction or persist for years. The presence of PLEDS, however, usually indicates recent infarction. PLEDS have been particularly associated with watershed ischemia (Chatrian et al., 1964). After intracerebral hemorrhage, slowing is commonly focal but can be diffuse in the presence of coma or multifocal in the presence of vasospasm.

The EEG is not reliable in predicting type, timing or recurrence of seizures after stroke and should not be used as the sole basis for prophylactic anticonvulsant therapy (Holmes, 1980; Luhdorf et al., 1986b; Bladin et al., 1996, 1998). In addition, there are considerable logistic difficulties in obtaining an EEG in ill patients with acute stroke.

30.9. Management

There is little information on the impact of anticonvulsant medication with respect to the risk of seizures associated with stroke. Fortunately, most stroke patients experiencing seizures within the first few weeks of stroke will not have another. Conversely, because of a higher likelihood of recurrence, to commence anticonvulsants after a second seizure would be appropriate in most cases. Observational studies with small numbers of patients suggest that an isolated early seizure after cerebral infarction either do not require treatment or can be easily controlled with a single drug (De Carolis et al., 1984; Shinton, 1988; Kilpatrick et al., 1990).

Newer anti-epileptic drugs have fewer side-effects and some are not liver metabolized with less drug interactions (e.g. warfarin). A prospective cohort study of gabapentin monotherapy in patients with late-onset

seizures (67% had epilepsy) found that 81% had excellent seizure control with no seizure recurrence after 30 months, but a control group was lacking (Alvarez-Sabin et al., 2002). However, beginning treatment after the early-onset seizures has not been associated with a reduction of recurrent seizures after discontinuing the medication (Gilad et al., 2001). Clearly, a first prolonged seizure or status epilepticus needs urgent therapy. A trial of anticonvulsant withdrawal is reasonable if a patient has been seizure-free for more than 2 or 3 years and is healthy enough to survive a recurrent seizure.

Patients who develop recurrent stroke seizures (epilepsy) generally require pharmacological treatment. An observational hospital-based study and a prospective cohort study showed that 54% and 67% of patients with epilepsy after cerebral infarction were seizure-free for at least 1 year with the majority of patients being treated with a single drug (Semah et al., 1998; Stephen et al., 2001). However there is no current data showing that use of anticonvulsant drugs after stroke, or indeed other acute brain injuries, prevents the later development of epilepsy (Herman, 2002).

Before commencing treatment one must weigh up the risks of anticonvulsant therapy in the individual patient, especially as many will be elderly and particularly susceptible to adverse drug reactions and interactions (Reynolds, 1975; Patsalos and Duncan, 1993; Scheuer and Cohen, 1993; Rambeck et al., 1996; Spina et al., 1996). Equally the elderly are particularly vulnerable to injuries sustained from seizures (Grisso et al., 1991).

30.10. Conclusion

Seizures following stroke are common and occur in about 9% of patients overall, especially in the first few weeks. Seizures are more common after cerebral hemorrhage than infarction. The risk of epilepsy following stroke for the individual is low, about 3%, yet still higher than the age-matched population. Because stroke is common in older age groups, post-stroke seizures and epilepsy are important community health issues. While there is limited understanding about the pathogenesis of seizures and epilepsy after stroke, it is clear that cortical location is a risk factor after both cerebral infarction and hemorrhage. Lesion size as such is a predictor only after cerebral infarction. A better understanding of the role of anticonvulsant therapy in the management and prophylaxis of post-stroke seizures and epilepsy is required to provide guidelines for management. Currently, there is little clinical experience with the newer anticonvulsants in this setting, but an extrapolation of available data from studies in epilepsy would suggest that they are likely to be of use in the future.

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Chapter 31

Stroke-related psychiatric disorders

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31.1. Introduction

Neuropsychiatry refers to the study of psychiatric disturbances following an organic lesion in the brain. The interest is towards behavioral changes, for which there is evidence of a causal connection with regional brain dysfunction. This causal relationship can be retained on the following basis: the association of the symptoms with brain damage and neurological and cognitive deficits is known to be statistically significant; the disorder represents a significant change from the prestroke condition; and it produces considerable distress in social, occupational, or other important functional areas.

Behavioral changes can correspond with the appearance of new symptoms but also with the exaggeration of premorbid personality traits, or they might vacillate between these two extremes. Thus, personality aspects, which were relevant before stroke, and the degree and the direction to which they have changed, should both be assessed.

Stroke is an important field of investigation in neuropsychiatry for the following reasons. Stroke is a disorder that has great prevalence; brain infarction involves, in most instances, defined vascular territories and psychiatric signs generally emerge in association with specific cognitive deficits (Table 31.1). In fact, the occurrence of a pure psychiatric condition (without other neurological signs) following stroke is an extremely rare event.

It should be clearly stated that factors challenging the assessment of neuropsychiatric disorders into an anatomoclinical foreground are many. The brain subdivision in vascular territories does not overlap its subdivision in functional systems. Such systems consist of multiple modules with diffuse reciprocal connections inside a matrix composed, in both hemispheres, by frontal, subcortical (basal ganglia, thalamus, brainstem) and limbic circuitries, and low and high-order uni- and heteromodal cortical associations areas. Therefore a single stroke may coincidentally involve several of these modules, areas, and systems or cause dysfunction of remote modules, areas, and systems when these become disconnected from the damaged ones. In other circumstances the lesion of single modules in one functional system may manifest with the dysfunction of the whole system. In other cases behavioral changes due to a focal lesion may be attributable, at least in part, to preserved areas. During recovery other areas can be recruited to compensate for the deficits. In addition, diffuse projection systems of specific neurotransmitters, which modulate basic processes of arousal (e.g., norepinephrine), attention (e.g., norepinephrine and acetylcholine), motivation (e.g., dopamine), and mood (e.g., serotonin), originate from subcortical nuclei and widely disseminate in the brain. The involvement of these systems may reduce the information-processing states and efficiency of specific systems, as behaviors and cognition require arousal, stable mood, and motivation.

As a result, the assumption that a certain area deserves a specific cognitive or behavioral function because that function is compromised after a stroke in that area may be questionable. Furthermore, the individual variability in vascular topography, hemispheric dominance, skill achievement and premorbid personality, and the possible co-occurrence of brain atrophy, leukoaraiosis, and degenerative lesions accumulating with age are other confounding variables to keep in account in the attempt to estimate the connection between behavioral changes and focal lesions.

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Table 31.1

Cognitive and behavioral syndromes reported with ischemic stroke in circumscribed vascular territories

	Cognitive syndromes	
Cerebral arteries	Right-side	Left-side
Middle cerebral artery (MCA)		
Complete MCA superficial territory	Left neglect. Anosodiaphoria. Constructive and dressing apraxia. Acute confusional state. Dysprosodia	Global or Broca's aphasia. Ideomotor apraxia
MCA superior or anterior division	Left neglect. Dysprosodia. Anosognosia of hemiplegia. Acute confusional state	Mutism evolving over few days in aphemia or in Broca's aphasia, bucco-linguo-facial apraxia. Wernicke's aphasia is very rare
MCA inferior or posterior division	Left neglect. Constructional apraxia. Delirium or confusional states. Sensory dysprosodia	Wernicke's aphasia. Conduction aphasia. Global aphasia
Orbitofrontal artery (usually associated with prefrontal and central artery territory infarction)	Unit or bilateral lesions: disinhibition, spontaneous confabulations	
Prefrontal artery	Delusions	Transcortical motor aphasia
	Bilateral lesions: loss of planning abilities, utilization and imitation behaviors, grasp reflex, perseverations, poor abstraction and categorization, reduced mental flexibility, apathy and abulia	
Precentral (prerolandic or precentral sulcus) artery	"Frontal" neglect	Transcortical motor aphasia and limb kinetic apraxia Global aphasia without hemiparesis (if there is a second lesion in the posterior language areas). Aphemia or pure apraxia of speech Pure anarthria. Transcortical sensory aphasia. Agraphia with or without acalculia
Central sulcus artery		Mild Broca's aphasia
Anterior parietal (or post-central sulcus) artery	Left neglect. "Acute hemiconcern"	Acute conduction aphasia being or not associated with ideomotor apraxia, anomia, acalculia or agraphia
Posterior parietal artery (usually in association with angular artery territory infarction)	Hemiextinction Visuospatial and visuoconstructive dysfunction	Wernicke's aphasia. Gerstmann's syndrome. Ideomotor apraxia Anomic aphasia. Phonologic agraphia
Angular artery	Spatial neglect. Hemiextinction. Asomatognosia. Visuoconstructive and visuospatial disturbancies	Gerstmann's syndrome. Transcortical sensory aphasia. Anomic aphasia. Wernicke's aphasia
	Bilateral lesions: Balint's syndrome sometimes associated with anterograde and partially retrograde amnesia	
Temporal arteries	Left visual neglect. Left-side extinction. Constructional apraxia. Agitated confusional state. Manic symptoms	Wernicke's aphasia Difficulties in identification of melodies or rhythm perception
	Expressive instrumental amusia	
	Bilateral lesions: cortical deafness that could be associated with delusions about time. Pure word deafness	

Lenticulostriate arteries:		
— Internal capsule, anterior limb	Infarcts affecting the anterior thalamic peduncle induce frontal lobe signs and motor neglect. Bilateral lesions: akinetic mutism	
— Upper part of the internal capsule and corona radiata adjacent to the lateral ventricle	Neglect or constructional apraxia	Aphasia
— External capsule —subinsular infarcts		Aphasia
— Lentiform nucleus	Micrographia	Aphasia and agraphia
— The head of the caudate nucleus	For right or left lesions: abulia, akinesia, frontal lobe signs (disinhibition, inappropriateness). Aphasia with left (sided lesions and neglect with right) sided lesions. Defective recall. Psychotic features. Mood changes. Dementia for bilateral lesions	
	Motor and visuo-spatial neglect. Visual memory dysfunction	Transcortical motor aphasia. Anomia. Verbal memory deficits
Striatocapsular infarcts	Neglect (good prognosis)	Aphasia (good prognosis)
Anterior cerebral artery		
— Cortical infarcts	Abulia or akinetic mutism which tend to be persistent in case of bilateral infarctions. Infarction in the mesial frontal lobe can cause emotional liability, euphoria, stuttering, mirror writing, grasp phenomenon.	
		Transcortical motor aphasia
— Corpus callosum	Signs of callosal dysconnection syndrome (left unilateral ideomotor apraxia, left-hand agraphia, unilateral tactile anomia, unilateral constructional apraxia of the right hand, bilateral crossed pseudoneglect, alien-hand sign, diagonistic dyspraxia)	
— Caudate infarcts (Heubner's artery)	See above: the head of the caudate nucleus in the ACM territory	
Anterior choroidal artery	In most cases without cognitive deficits.	
(Deep branch of ICA)	Visual neglect, constructional apraxia, anosognosia and motor impersistence	Thalamic aphasia. Slight language processing difficulties and short-term verbal memory deficit
Posterior cerebral artery (PCA)		
Superficial PCA-territory	Neglect Constructional apraxia Topoagnosia	Alexia without agraphia and anomia for colors or color agnosia or achromatopsia. Elements of Gerstmann's syndrome. Elements of conduction aphasia. Anomic aphasia. Transcortical sensory aphasia. Visual agnosia. Persistent amnesia
Bilateral infarction in the superficial PCA-territory	Bilateral inferior bank infarcts: amnesia. Prosopagnosia. "Ventral" agnosia. Bilateral superior-bank infarcts: Balint's syndrome, difficulty in re-visualizing directions. "Dorsal" agnosia.	
Proximal PCA disease with thalamic infarction	The clinical findings are those of the lateral thalamic infarction due to the occlusion of the thalamogeniculate or posterior choroidal arteries combined with temporal and occipital deficits including anomia, transcortical sensory aphasia or visual neglect.	
Thalamic infarcts		
Thalamo-geniculate arteries	Cognition and behaviors are generally preserved	
Infarcts in the territory of the polar artery	Abulia. Appatia. Akinetic mutism. Loss of self-psychic-activation. Acute amnesia. Verbal-recall impairment is more common with left-side infarcts, whereas visual-memory deficits predominate in those with right-side infarcts. Bilateral infarcts: abulia and amnestic disturbancies are severe and persistent.	
Paramedian thalamic-subthalamic arteries	Hypersomnolence, lethargy, amnesia, confabulations. Bilateral infarcts: cognitive impairment is more severe and long-lasting, utilization behavior, palypsychism.	
Posterior choroidal artery	Aphasia, amnesia, abulia and visual hallucinosis	

Adapted from Bogousslasvky and Caplan, 2001 by the original authors.

Another diagnostic difficulty is due to the co-occurrence of emotional changes with cognitive changes. Cognitive deficits (aphasia, neglect, bradypsychism) may diminish the reliability of answers in standardized interviews but also affect the patient's insight into his own emotions and behaviors. The assessments of patients with severe comprehension deficit could be particularly difficult even with analogical scales. Dysprosodia, bradypsychism, and apathy could be confused with depressed mood. Apathy and irritability could be behavioral correlates of a dysexecutive syndrome. Paranoid ideation for patients with fluent aphasia could be secondary to verbal deafness-like deficits and related lack of insight. Post-stroke emotional and mood disorders may not only associate with cognitive deficits but also cause them (for example, through lack of motivation and poor effort during assessment). Therefore detailed neuropsychological examination including tests assessing the patient's effort, is necessary to specify the nature and severity of cognitive deficits, their relationship with emotional changes, and to plan adequate rehabilitative treatments.

Psychiatric changes may be also subtle, fluctuating in time or manifesting in specific social contexts. The experience and the expression of emotion may dissociate. For example, crying and laughing may not correspond to feelings of sadness and joy in patients with pathological crying; depressive feelings might be evident in behaviors yet verbally denied by patients who are anosognosic of, or deny, their depression (Biran and Chatterjee, 2003).

Patients often minimize irritability or aggressiveness, even if these behaviors diminish their autonomy and alarm those close to them. These difficulties of assessment explained as psychiatric conditions are often underestimated and undiagnosed after stroke, despite their high prevalence.

Finally the assumption of a causal relationship between psychiatric changes and stroke (according to criteria defined above) appears to be particularly evident for only a few disorders, such as misidentification syndromes, anosognosia of hemiplegia, mania and habit changes (conditions related to right hemisphere dysfunction), apathy, and emotional lability (conditions related to dysfunction of frontal–subcortical and limbic circuitries). For these syndromes another argument that may favor a causal connection between focal brain damage and behavioral changes, besides the typical clinical presentation with that lesion, is the evidence that symptoms are more severe in the earliest phase of stroke when stroke-related variables (edema, lesion localization) make neurological and cognitive deficit more evident before processes of neural plasticity intervene to facilitate recovery.

Conversely, the role of the ischemic lesion is not so rigorously established for disorders (such as depression and anxiety) in which the development is often gradual and late (after the first 3 months post-stroke), the clinical presentation is not stereotypical, and for which the course and the response to treatments have a variable temporal profile. These characteristics of these disorders could be due to the intervention of non-stroke related variables such as the psychological or psychosocial processes of coping with the disease. However, for these reasons, the usual co-occurrence of behavioral changes with cognitive deficits (for example depression with aphasia, or anger with executive dysfunction) that point to the dysfunction of specific neural systems could be a useful key in understanding the neural underpinnings of such disorders. Therefore neuropsychiatric research should be designed with the supplementary intent of defining cognitive models of emotional regulation.

In the last two decades the use of more sophisticated cognitive and behavioral instruments (particularly for executive functions, mentalizing, and empathy) improved the clinical assessment of behavioral disorders. At the same time, the application of sophisticated paradigms to functional neuroimaging permitted more accurate delineation of neural networks charged with emotional processing.

Several recent studies have focused on personality and specific behavioral changes (such as independence, patience, energy, enthusiasm, etc.) emerging after stroke (Stone et al., 2004). Such observations are also of interest in neuropediatry; for example, children with cerebral palsy were reported to show a high relative risk (approximately 50%) of psychiatric symptoms such as hyperactivity, conduct disturbances, aggression, and oppositional behaviors (Goodman and Graham, 1996). Actually, a multidisciplinary approach, integrating neurological, psychiatric, neuropsychological, neurophysiological and neuroradiological data, is the most useful not only for diagnoses but also for investigating post-stroke emotional disorders.

Here we present adult neuropsychiatric syndromes that follow ischemic stroke, as they are more frequent and typified by infarction of defined vascular territories than with other vascular etiologies. This presentation will be carried out according to four axes: (1) affective or mood disorders; (2) behavior or personality disorders; (3) cognitive disintegration (acute confusional state); and (4) disorders of the perception-identification of the self, other people, places, and time (systematic delirium). This classification is purely empirical but permits simplification and probably has pedagogical and theoretical foundation.

31.2. Affective and mood disorders

31.2.1. Post-stroke depression

Although methodological differences occur among studies, epidemiological research has showed a very high prevalence of post-stroke depression (PSD) among stroke survivors (about 30%; for a review see Carota and Bogousslavsky [2003]). Major depression accounts for approximately 30% and minor depression for about 70% of cases of PSD.

In fact the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) (American Psychiatric Association, 2000) provides criteria that are considered the gold standard by the scientific community. For a major depressive episode, the DSM-IV requires the persistence of symptoms for at least 2 weeks. Thus, in many cases PSD cannot be formally diagnosed during the first admission to the hospital. DSM-IV criteria correspond to the depression occurring with chronic medical conditions (e.g., chronic heart failure, hyperthyroidism, stroke). The only feature distinguishing PSD from depression of subjects without brain damage (i.e. endogenous depression) would be a persistent depressed mood that is judged as one of the direct consequences of a general medical disorder. Therefore, the DSM-IV criteria for PSD diagnosis are prone to several critics. For instance, they are based on the assumption that a unique dimension exists where all the depressive symptoms (dysthymia, melancholia, anhedonia) are represented in a continuum with different degrees of severity. Within this unidimensional perspective, premorbid personality traits (such as depressive temperament and neuroticism) are irrelevant to diagnosis. Moreover, it is unclear why a presupposed etiological factor for PSD (e.g., stroke) should exclude the diagnosis of a depressive disorder such as endogenous depression that simply occurs after stroke. Thus, in clinical research, the DSM-IV criteria themselves might contribute to bias patterned sampling of patients with PSD.

Furthermore, somatic symptoms (fatigue, sleep disturbances) and cognitive symptoms (memory and attention deficits, reduced thinking, and speech) of PSD contemplated by the DSM-IV are frequent among stroke patients even in the absence of depression. Therefore some authors considered that "non-reactive" or "unmotivated" symptoms of the depressed mood (e.g., feelings of worthlessness, guilt, and suicidal ideation) are specific for endogenous depression, whereas "reactive" or "motivated" aspects (low mood, reduced appetite, and anergia), anxiety, and vegetative signs are the clinical hallmarks of PSD (Gainotti et al., 1999). These authors suggested that "unmotivated" aspects are conditioned by neurobiological factors while "motivated" symptoms are due to the process of coping with disability.

The distinction of the DSM-IV between major and minor depression is another source of criticism. This distinction has been configured for PSD in terms of the "continuum" versus the "categorical" hypothesis. The "continuum hypothesis" posits that major and minor forms of PSD are expressions of the same disease, differing only in the severity of symptoms (Gainotti et al., 1997a). This continuity has been interpreted as a psychological reaction that parallels the degree of disability, and has therefore a psychodynamic foundation. Conversely, the "categorical" hypothesis posits that major and minor forms of PSD have different causes, and that the most determinant factor of major depression is stroke location (Morris et al., 1994).

Leaving DSM-IV criteria out of consideration, the diagnosis of PSD still remains a difficult task because of the interference of other variables. Cognitive changes may compromise the validity of patients' answers during a psychiatric interview. Even when language and attention are not impaired, patients may still fail to respond in a reliable fashion (Toedter et al., 1995; Price et al., 1999), therefore, the validity of replies should be accurately assessed. Furthermore, it is essential to consider carefully whether a "depressed response" might be a neurological symptom (Table 31.2).

However, standardized scales and questionnaires of depression are important clinical tools because they allow reproducible diagnoses among different studies, and monitoring of the effects of therapeutic interventions. The most used are the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960), the Beck Depression Inventory (BDI) (Beck et al., 1961), the Hospital Anxiety and Depression scale (HAD) (Zigmond and Snaith, 1983), the Zung Self-Rating Depression scale (ZSDS) (Zung, 1965), and the Montgomery–Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979). The MADRS shows greater sensitivity to change and can differentiate between those who respond to antidepressant treatment and those who do not, probably better than the HDRS and BDI.

Even if those questionnaires show concurrent validity for endogenous depression and PSD (Agrell and Dehlin, 1989; Aben et al., 2002b), there is evidence that lower cut-off scores may be more adequate for PSD in comparison to endogenous depression (Naarding et al., 2002) but these data are not univocal (Lincoln et al., 2003).

The Post-Stroke Depression Scale (Gainotti et al., 1997b) assesses depressive symptoms (especially somatic symptoms) or other conditions (e.g., catastrophic reaction and emotionalism) retained as more

Table 31.2

Diagnostic confounders of depression in stroke

Indirect
Common to many severely ill hospitalized patients
Controlled appetite (e.g. NPO and tube feeding)
Frequently awakened
Confined to bed
Delirium (acute confusional states)
Of special concern in stroke patients
Immobility (potential confusion with apathy)
Dysphagia (interferes with eating habits)
Slurred speech (and resultant miscommunication)
Fatigue
Direct
Aphasia
Amnesia and cognitive impairment
Anosognosia
Aprosody
Neurological apathy syndromes
Isolated abulia/apathia
Loss of psychic auto-activation
Frontal lobe syndrome
Klüver-Bucy syndrome
Korsakoff's syndrome
Post-stroke fatigue
Disorders of emotional expression
Pseudobulbar syndrome
Emotional lability or emotionalism
Catastrophic reaction
Dementia

specific to patients with depression occurring in the context of brain damage. This scale does not supply cut-offs but provides a clinical profile of PSD. The Stroke Aphasic Depression Questionnaire (Sutcliffe and Lincoln, 1998), the modified Analogue Dysphoria Scale (Stern and Bachman, 1991), and the Visual Analog Mood Scales (VAMS) (Arruda et al., 1999) could be useful tools for screening depression in patients with aphasia.

In the last 30 years, about 300 clinical studies were carried out to provide insight into neural systems involved in PSD. Most studies assessed the role of lesion location by MRI and CT scan in encountering patients with and without PSD. Unfortunately, data for these studies were inconclusive. Initially, a large number of clinical studies by Robinson et al. (see Robinson, 1998) suggested that lesion location in the left hemisphere and proximity to the frontal pole were the most important predictors of a major depressive episode after stroke. Damage of the biogenic amine-containing pathways, which have a more anterior cortical distribution, was considered to be the neurobiological substrate. This localization model of PSD has been greatly criticized. For instance, diffuse lesions in the middle cerebral artery territory are often proximal to both poles. Furthermore, only small samples of patients were analyzed (even less than 30–45 subjects) and patients with severe aphasia were excluded. Other studies failed to find any lateralization or any anterior–posterior gradient (House et al., 1990a; Andersen et al., 1995; Ng et al., 1995; Gainotti et al., 1997a; Herrmann et al., 1998; Paolucci et al., 1999) while others found that right hemisphere damage was associated with PSD (MacHale et al., 1998). Other authors suggested that depression might be associated with an asymmetric mode of hemisphere functioning only if co-occurring with a generalized anxiety disorder (Heller et al., 1995).

In subsequent papers, Robinson et al. (Shimoda and Robinson, 1999) proposed that PSD was related to left frontal and basal ganglia stroke in the acute phase, to an anterior location either in the left or the right hemisphere when PSD occurred several months after stroke, and to right posterior lesions when PSD manifested 1–2 years after the stroke.

A recent meta-analysis, by reviewing 35 studies (108 being excluded for methodological problems!) concluded that lesion location might contribute to PSD only to a small extent (Carson et al., 2000). Another meta-analysis of 26 studies still found an association between PSD and lesion location on the left hemisphere (Bhogal et al., 2004). However, this association might have depended either on some demographic characteristics (i.e. being an in-patient) or the interval after stroke onset (i.e. assessment of depression within a few weeks post-stroke). A further meta-analysis, adopting different selection criteria, supported a relationship between the proximity of the lesion to the left frontal pole and the risk of PSD (Narushima et al., 2003). The few neuropathological data available did not allow the identification of specific stroke locations for PSD in elderly patients (Bozikas et al., 2005). In fact, no definite conclusions can be drafted by meta-analysis.

However, an important argument promoting the role of frontal and anterior brain regions in determining PSD is that depression is one of the most relevant clinical and often initial symptoms of other neurological disorders of which the lesions are located within frontal–subcortical circuitries (subcortical vascular dementia, CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), HIV-related dementia, Huntington's disease and Parkinson's disease). In conclusion, the causal relationship between lesion location and pathogenesis of PSD remains unproven. Conversely it is

certain that lesion location has poor clinical utility in determining which patients should be screened for PSD.

A significant association between PSD and cognitive deficits has been reported in several studies, even though stroke itself may be followed by a significant decline in cognitive performance when prestroke and post-stroke measurements are compared (Henon et al., 2001). The question is whether it is depression that causes cognitive impairment ("dementia of depression") or whether cognitive impairment leads to depression ("depression of dementia"). The answer is probably that the link runs both ways. Actually there is not a specific cognitive profile that could distinguish PSD from endogenous depression; however, the presence of aphasia can increase the risk of major depression after stroke. Conversely, other community studies using the MMSE (House et al., 1990a) or other measurements (Kase et al., 1998), did not establish, in the chronic phases of stroke, a correlation between cognitive impairment and major depression.

In PSD, diminished physical or cognitive functioning inevitably produces conflicts with significant others; there may be isolation, loss of professional role, the need for medical and rehabilitative programs and environmental changes, and financial problems may ensue. These factors are certainly a source of anxiety for the stroke survivor. In this psychological dimension of reactive depression, a specific profile of symptoms can be frequently observed: patients complain about their difficulties and the environment, show self-pity, feel that others are guilty, often report somatic symptoms that are the source of obsessions and intrusive thoughts. On the contrary, the main symptom of a "non-reactive" depression is anhedonia (a decreased experience of pleasure or interest in previously enjoyed activities). Therefore bias in selecting patients (i.e., failure in discriminating between patients with "reactive" or "non-reactive" PSD) could be a reason for the inconclusive findings on the role of lesion location. Beck's cognitive theory of depression argues that negative automatic thoughts, generated by dysfunctional beliefs, are the cause of depressive symptoms and not vice versa (Beck et al., 1979). This theory is appealing because it configures depressive symptoms into a cognitive dimension of disturbed emotional regulation, describable in terms of neural circuitries. However, there are no models of brain functioning that sufficiently explain the respective roles of organic (related to the lesion) and psychological (related to coping) factors in the emergence of depressive symptoms.

An aspect of PSD emerged from cohort studies as more certain than doubtful: the severity of the neurological deficits or disability at stroke onset or during recovery is the variable that most correlates with PSD occurrence (Singh et al., 2000; Naess et al., 2005). However, once again, this correlation may be the effect of both psychological (the affective reaction is proportionate to the severity of the deficit) and biological causes (a more extended lesion is more likely to damage the brain areas implicated in mood regulation). In a prospective study including 273 stroke patients assessed in the first few days after stroke, the emotional lability and severity of neurological deficits (measured with the Barthel Index) resulted in predictors of PSD that were more significant than stroke location (Carota et al., 2005). Therefore research on crying (an overt behavior more easily measured) could provide further insight into the neurobiology of depressive symptoms.

The scientific interest in PSD pathogenesis remains high because it is plausible that identifying neural mechanisms of PSD would permit better comprehension of endogenous depression (ED) causes. Recent discoveries in the domain of the cognitive control of emotion—reviewed by Ochsner and Gross (2005)—open a new field of investigation for PSD. This field is particularly promising in its attempt to unify "organic" (related to the stroke location) and "psychological" (related to coping) factors in cognitive models that have neural and/or biochemical correlates.

There is strong evidence that PSD has a negative repercussion on recovery of neurological deficits (Pohjasvaara et al., 1998), functional autonomy (Singh et al., 2000) and quality of life of the patient (Haacke et al., 2006). Furthermore, PSD is one of the most significant determinants of the caregiver's depression (Berg et al., 2005), a disorder with 30% prevalence.

These last aspects suggest that pharmacological treatment should be always considered for PSD, especially for patients with severe neurological deficits even in the first weeks after stroke before transfer to the rehabilitation center. Pharmacological treatments of PSD might also reduce the overall risk of mortality of stroke patients (Jorge et al., 2003). Although this finding should be confirmed in future research, it should be noted that depressive symptoms have been recognized as a risk factor for both cardiovascular disease and stroke (Gump et al., 2005).

The recovery from depression is considered significant when it corresponds to a reduction in the score of standardized questionnaires (i.e. the HDRS or BDI) greater or equal to 50%, and the use of scales (such as MADRS) is specifically required to monitor therapeutic interventions. However, 50% or greater reduction of depressive symptoms might not correspond with disease remission. Furthermore, as generally

accepted, a placebo effect may also account for 30% of the therapeutic responses in trials of antidepressants. The evidence for the efficacy of nortriptiline, citalopram, and fluoxetine in treating PSD emerges from few controlled studies (Andersen et al., 1994; Robinson et al., 2000; Fruehwald et al., 2003). Actually, recent Cochrane reviews concluded that data are not sufficient to propose pharmacological drugs for both prevention and treatment of PSD (Anderson et al., 2004; Hackett et al., 2004). However these conclusions have poor clinical implication, because (for the reasons reported above) depressive symptoms should always be treated early and intensively in stroke patients.

Selective serotonin reuptake inhibitors (SSRI) are the first choice of drugs because of their safety profile. According to expert recommendations, a pharmacological treatment should be continued for at least 4–6 months. Cognitive and behavioral therapies could be appropriate treatments, especially in those cases where vegetative and somatic signs are not prominent, and depressive symptoms and personality traits have been assessed extensively. However, definitive data on these therapies are not yet available for PSD.

31.2.2. Vascular depression and vascular dementia

The evidence in geriatric populations of a significant association between the development of a depressive syndrome and the presence of vascular lesions in the white matter (especially in frontal regions) and basal ganglia suggests the existence of a depression of vascular origin (related to small-vessel disease and not to stroke in its more general clinical acceptation) (Greenwald et al., 1998; Steffens and Krishnan, 1998). Patients affected by this form of depression present several vascular risk factors (especially hypertension), manifest moderate cognitive deficits (specifically reduced mental control and executive dysfunction) and behavioral changes (apathy), and less favorable response to antidepressant drugs (Alexopoulos et al., 1997; Simpson et al., 1998).

This concept of vascular depression is based on descriptive criteria and is therefore particularly prone to methodological bias. Nevertheless, its scientific interest remains high. In fact, the association of vascular risk factors, vascular brain lesions, cognitive symptoms, and depressive mood depicts for vascular depression a complex picture where each of these factors can progressively increment the others, which can in turn accentuate the symptoms in a "spiral" of cause and effect (Dieguez et al., 2004). The presentation of mood disorders in elderly patients, especially in the context of motor deficits (such as gait difficulties, lower body parkinsonism, and dysarthria) induces the search for white matter and basal ganglia vascular lesions.

Vascular dementia is the second most common cause of dementia (25–30% of all dementias) (Roman, 2003) although its prevalence is probably underestimated because of its frequent association with Alzheimer's disease. In fact, vascular dementia includes several disorders (micro- and large-vessel diseases, recurrent or strategic strokes, chronic hypoperfusion) (Wallin et al., 2003). Thus clinical signs of vascular dementia are related to both localization and number of strokes.

In subcortical vascular dementia lesions are located in the periventricular white matter, basal ganglia, and thalamus (Roman et al., 2002). Resultant cognitive deficits are a reduction in mental speed, and attention and memory (free recall more than recognition) disturbances (Graham et al., 2004; Price et al., 2005). On the neuropsychiatric side, patients with vascular dementia show overt depressive signs, emotional lability, irritability, and apathy (O'Brien, 2003). The prevalence of disorders of mood and emotional expression is higher in patients with vascular dementia than in patients with Alzheimer's disease (Newman, 1999). The cognitive and behavioral profile of subcortical vascular dementia is similar to other subcortical dementias and all of them differentiate from Alzheimer's disease for the presence of motor signs such as gait apraxia/ataxia and dysarthria.

The overall clinical picture of patients with subcortical vascular dementia points to the dysfunction of frontal–subcortical circuitries (Looi and Sachdev, 2000). However, it is not yet possible, inside these circuitries, to define precise lesion locations for specific behavioral changes. Vascular lesions are generally multiple and involve several functional systems. Furthermore, behavioral and mood changes may reflect the loss of cerebral volume more than specific lesion localizations. Other interfering variables are the individual variability of the cognitive reserves in elderly patients and the possibility that hippocampal atrophy and amyloid precursor protein (APP) overexpression (pathological hallmarks of Alzheimer's disease) can be even enhanced by vascular insufficiency (Sadowski et al., 2004).

31.2.3. Affects and mood of patients with aphasia

After stroke, patients with aphasia might manifest several intense emotional changes. A classic model of neuropsychiatry postulates the existence, within the dominant hemisphere, of an anterior–posterior gradient as regards to the Rolando fissure (Benson, 1973;

Signer et al., 1989). According to this model, patients with anterior lesions, frequently with Broca's aphasia (nonfluent aphasia with agrammatism, paraphasic errors in spontaneous language and repetition, and relatively sparing of comprehension), show more depressive symptoms. Actually, there is evidence that nonfluent aphasia is a risk factor for PSD (Kauhanen et al., 2000). Conversely, patients with posterior lesions and fluent aphasia such as Wernicke's aphasia (verbal paraphasias in spontaneous speech and repetition, poor comprehension) often display restless behaviors such as euphoria, psychomotor agitation, aggressiveness, and delirium. This last category of patients probably does not have sufficient insight (anosognosia) into linguistic difficulties (they do not understand that they do not understand). Such a situation is presumed to induce paranoid ideation (not verbally mediated), which would translate into agitated behaviors.

For patients with nonfluent aphasia, relatively spared comprehension and awareness, depressive symptoms might be related to an understandable psychological reaction to linguistic deficits. These patients do not know how to cope with the frustrating condition of being unable to communicate. The catastrophic reaction of aphasic patients (Goldstein, 1952) represents an extreme degree of frustration. At the moment of executing a linguistic task, the patient, rather suddenly, with mounting feelings of frustration and depression and then of hostility, breaks into labored sobbing and weeping, often accompanied by phrases, sounds, or gestures that indicate both hopelessness and anger. The patient refuses to carry on with any language procedure or even with simple conversation. The sobbing may last many minutes and negativism for considerably longer (Benson, 1973). A semiquantitive scale (the Catastrophic Reaction Scale) has been specifically constructed to assess catastrophic reaction (Starkstein et al., 1993a). However, the scale relies mostly on verbal cues and is difficult to apply to patients with severe comprehension deficits. The incidence of catastrophic reaction in stroke, adopting that scale, corresponds to approximately 10–20% (Starkstein et al., 1993b). Adopting only observational measures, catastrophic reaction was reported in 12/326 (3.7%) of patients with first-ever stroke within the first 3 days of the onset of stroke (Carota et al., 2001). In this study, all patients with catastrophic reaction were aphasic. The association of catastrophic reaction with aphasia has been interpreted in terms of a psychological reaction because the inability to effectively express oneself may be one of the most emotionally burdensome consequences of stroke (Teasell, 1993). However, the abnormal emotional content of catastrophic reaction and its typical character are also arguments for a lesion-induced neural dysfunction. A catastrophic reaction develops when the performance is requested, sometimes even before the slightest attempt, hence catastrophic reaction could correspond to a reflex avoidance behavior more than to a conscious response to task failure.

Left hemispheric damage predisposes to catastrophic reactions, a finding already claimed by studies including stroke patients (Gainotti, 1972, 1976; Starkstein et al., 1993b; Carota et al., 2001), as do normal subjects and epileptic patients subjected to left carotid sodium amytal injection (Terzian and Ceccotto, 1959). These findings support the theory of left hemisphere specialization in enhancing emotional behaviors with social communicative purposes, whereas withdrawal-related emotions may be preferentially treated in the right hemisphere. A catastrophic reaction may be the behavioral translation of "paleological thinking," emerging from homologous areas of the right hemisphere when language areas are damaged in the dominant one. Patients with a catastrophic reaction could shift from a left to a right mode of limbic processing. This hypothesis has already been proposed to explain the aggressiveness of patients with Wernicke's aphasia (Ross, 1996). The critical issue is to define the neuroanatomical substrate, within the left hemisphere, that links a linguistic task to the catastrophic reaction.

As previously noted, an essential corollary for aphasic patients is that the assessment of mood, affects, emotion, personality, and inner experiences is an extremely difficult task, even adopting analogical or nonverbal scales (Price et al., 1999; Turner-Stokes, 2003). Often it is necessary to rely on observational measures and on the narratives of caregivers or nurses. The unavailability of adequate measures probably explains the paucity of research in the neuropsychiatry of aphasia in both early and late phases of stroke.

31.2.4. Post-stroke mania

According to the DSM-IV, symptoms of secondary mania (i.e., related to stroke or other medical disorders) are inflated self-esteem or grandiosity, sense of optimism and invulnerability, decreased need for sleep, distractibility, racing thoughts and pressured speech, and excessive involvement in pleasurable activities with potentially painful consequences (DSM-IV, 2000). In the most severe cases mania can manifest with psychotic symptoms. Conversely, hypomania represents a less severe manic state, does not produce psychotic symptoms and does not lead to major impairment in social or occupational function. Cycles of full-manic and depressive episodes correspond with bipolar I disorder

(BPI), whereas cycles of hypomanic and depressive episodes occur with the bipolar II disorder (BPII). However, secondary hypomania and secondary mania, with or without psychotic symptoms, probably correspond to a continuum (with increasing severity) within the same disorder. Furthermore, the psychiatric literature suggests that there is a continuum between affective disorders and schizophrenia, and that schizo-affective disorders, sharing more similarities with affective disorders than with schizophrenia, may be a link between them. Besides the categories of mania and bipolar disorder, the DSM-IV classification offers two other entries for manic symptoms: personality disorders (aggressive type) and impulse control disorders. In stroke literature, manic-like behaviors have been also described in terms of disinhibition syndrome, acquired sociopathy, pseudopsychopathy, and frontal lobe syndrome; terms that may engender confusion when comparing different studies. If differences in brain dysfunction exist between patients with post-stroke mania (PSM) and patients with post-stroke bipolar disorder, pure mania, or disinhibited behaviors, then this should be clarified.

The incidence of mania in acute stroke is very low, about 1% (Robinson et al., 1988; Starkstein et al., 1991). However, silent cerebral vascular lesions have been frequently detected in patients without psychiatric history who develop mania after 50 years (Fujikawa et al., 1995). Furthermore patients with PSM might have greater subcortical atrophy and family history of affective disorders than patients without mania (Robinson et al., 1988; Starkstein et al., 1988a; Starkstein and Robinson, 1997). Manic behaviors generally emerge with vascular lesions of frontal and temporal lobes, caudate nucleus (Starkstein et al., 1991), thalamus (Cummings and Mendez, 1984; Vuilleumier et al., 1998) and basal ganglia, generally on the right hemisphere (Cummings, 1986; Starkstein et al., 1988b, 1991; Berthier et al., 1996). Therefore manic behaviors are exceptionally isolated after stroke but generally occur associated with other neurological or cognitive deficits.

Patients with ischemic infarcts limited to the thalamus present significant memory disturbance and signs of dysexecutive syndrome. The clinical features of the three behavioral syndromes of the frontal lobe all may contemporaneously manifest in patients with thalamic stroke, usually after recovery of consciousness (Fukutake et al., 2002). Indeed, the mediodorsal nucleus is a central associative relay for all three frontosubcortical systems involved in emotional regulation.

In a PET scan study of three patients with PSM, all three were found to have hypometabolism in the inferior temporal regions of the right hemisphere (Starkstein et al., 1990b), which suggested as a mechanism for PSM the dysfunction of a frontal–striatal–capsulothalamic–cortical loop connected with temporal areas, a network with probable right hemispheric dominance (Starkstein and Robinson, 1997).

Regard and Landis (1997) described a non-disabling mania consisting of hyperphagia, with a specific preference for fine food ("Gourmand syndrome") in which predominant lesions involve the right frontal lobe basal ganglia and limbic areas. Such patients had usually right frontal strokes, spatial memory problems and diminished control over impulsive behaviors. Interestingly they did not become fat.

The prevalence of right hemispheral lesions in cases of PSM could be interpreted in light of the motivational direction model (Davidson, 1992) or the approach–withdrawal concept (or fight–flight freezing system) (Gray, 1994). These models postulate that the left and the right anterior regions of the brain are part of two separate neural systems mediating motivation, enhancing withdrawal or impulse toward action, respectively. Dysfunction of the right lateral anterior regions implies the loss of motivated withdrawal reactions to emotional stimuli and produces disinhibited behaviors. Conversely, the dysfunction of the right orbital–frontal system produces manic symptoms as a consequence of lack of affective empathy and rules of socialization.

Most patients with PSM reported in the literature have been treated with drugs used for primary mania (lithium, valproate, carbamazepine, lamotrigine, quetiapine, risperidone, olanzapine). However, whether these treatments are equally effective for PSM has not been proven. PSM is probably more difficult to treat than mania without brain damage, because stroke patients are more prone to epilepsy and secondary effects of drug therapies. In the elderly lithium has probably the most reduced benefit–tolerability profile.

31.2.5. Post-stroke generalized anxiety disorder

Generalized anxiety is an emotional state involving physiological arousal (increased heart rate), verbal reports of feelings of distress (e.g., apprehension and worry), overt behavior (e.g., avoidance), and cognitive disruption (i.e., maladaptative shifts in attention due to off-target thinking, hyperawareness about possible threatening cues in the environment, or the perception that adverse events are occurring in an unpredictable and uncontrollable manner). Worries may concern physical, mental, or social incapacitation and project both on the present and the future.

DSM-IV diagnostic criteria for post-stroke generalized anxiety disorder (PGAD) (DSM-IV, 2000) are for

anxiety occurring with a chronic medical condition, corresponding in turn to the criteria of anxiety of patients without brain damage. The incidence of PGAD is probably lower than that of post-stroke depression; about 20–25% in the first months (Castillo et al., 1993, 1995; Leppavuori et al., 2003) decreasing only slightly at 1 and 3 years follow-up (Astrom, 1996). In stroke patients, anxiety is frequently associated with depression. The association of anxiety and depression could be more frequent when neurological impairment is severe (Schultz, 1997). Patients with anxious personality and a history of prestroke psychiatric disorders could be more predisposed to PGAD. It is important to note that standardized questionnaires employed to screen anxiety and depression (such as the Hamilton anxiety–depression rating scales) could be particularly sensible to the degree of stress of the patients more than to depression or anxiety syndromes, and this could be a diagnostic bias (Schramke et al., 1998). The majority of clinical studies on stroke patients have looked for a disorder of generalized anxiety. Conversely, few data exist (Burvill et al., 1995) on the prevalence of anxiety-related disorders such as panic disorders, agoraphobia, specific phobias, and obsessive–compulsive disorder. PGAD shares many features with post-traumatic stress disorder. Both of these conditions can be considered to be the consequence of a sudden and unpredictable life-threatening stressor. The prevalence of post-traumatic stress disorder is approximately 10% in stroke patients (Sembi et al., 1998), compared with approximately 1–2% in the general population.

Maladaptive coping with the consequences of stroke can influence PGAD similarly to depressive symptoms in patients with post-stroke depression. Stroke patients may worry about losing control in social contexts because of their deficits (sensorimotor, cognitive, emotional). On the other hand, neurobiological factors of PGAD are poorly determined. Existing data about the relationship between anxiety and stroke location are not conclusive. Anxiety with no concurrent depression could emerge after right cortical lesions while the association of anxiety with depression could be the consequence of left cortical damage (Castillo et al., 1993; Astrom, 1996). In another study on a limited stroke sample, patients with post-stroke anxiety had more cortical lesions, while patients with combined anxiety and depression had more subcortical lesions (Starkstein et al., 1990a). However, the reproducibility of these results should be assessed.

There are no specific studies on pharmacological treatment of post-stroke anxiety. Treatment is essentially based on SSRI because of their better tolerability profile. Benzodiazepines should be avoided because of their negative effects on recovery and cognitive function in stroke patients (Troisi et al., 2002) and in animal models of stroke recovery (Goldstein, 1998).

31.2.6. Post-stroke emotionalism

Post-stroke emotionalism (PSE) has a high prevalence varying from 15% to 35% of stroke patients (House et al., 1989; Kim and Choi-Kwon, 2000). Although available data are not sufficient to delineate the natural course of this disorder, an increase in prevalence seems to parallel the amount of time elapsed since stroke onset, at least during the first 6 months (Ceccaldi et al., 1994; Kim, 1997a, b). PSE includes pathological laughter and crying (PLC), and emotional lability (EL).

The Pathological Laughing and Crying scale (Robinson et al., 1993), the Emotional Lability Questionnaire (Newsom-Davis et al., 1999), and the Center for Neurologic Study-Lability (Moore et al., 1997) are standardized self-rating scales that assess, for patients with PLC/EL, most of the variables involved (frequency, duration of episodes, relation to external events, degree of voluntary control, congruence with mood state and subsequent distress).

PLC and EL share the following attributes: an increase in the frequency of crying (shedding tears, sobbing) or laughing episodes in comparison to the patient's condition before stroke; onset with little or no warning; and the patient feeling that emotional expression goes beyond the normal control so that the patient may cry or laugh in social contexts which previously he or she would have considered to be inappropriate (House et al., 1989). Finally, crying and laughing are not only more frequent in patients with PLC and EL than in healthy people but are also more intense or excessive than simply a few tears or smiles.

PLC differs from EL on the basis of a few clinical features. The reflex quality of PLC is suggested by its emergence with little or no latency after irrelevant stimuli and by the frequent absence of congruence between emotional expression and internal affect. For instance, PLC can occur during relatively unemotional situations such as normal conversations, physical exercise, and repeated medical examinations or even be triggered by ocular movements or unexpected sounds (e.g., the telephone ringing). The diagnosis of PLC is based on these four characteristics: (1) the behavior is triggered by unspecific stimuli; (2) lack of relationship between the emotional expression and affective changes; (3) the absence of a corresponding change in mood during or lasting beyond the actual laughing and crying; and (4) the difficulty (perceived by the patient as severe) in controlling his own facial expressions while laughing and crying (Poeck, 1969).

In the case of EL, crying and laughter are generally provoked by stimuli with emotional significance (the visit of a relative, seeing a child) and, although the behavior occurs abruptly and is experienced as uncontrollable, the patient feels congruent emotions (joy or pleasure in the case of laughing and sadness or discomfort in the case of crying).

These general definitions point to the hypothesis that the neural mechanisms of PLC and EL can be different; that is, for PLC, a defective control of the motor acts of crying and laughing, and for EL a defective control of both the emotional experience and expression. However, these assumptions remain speculative because they have not been the object of specific investigations. Furthermore, the distinction of PLC from EL only on the basis of the congruence between trigger stimuli and internal feelings is often clinically difficult and impractical. For these reasons it has been proposed to include PLC and EL under the unique label of post stroke emotionalism (PSE) (House et al., 1989). It is also unknown in healthy individuals whether neural systems of crying and laughter are the same, to what extent they overlap and whether they are subjected to the control of similar cognitive processes.

In 1924, S.A.K. Wilson formulated a general theory on the neural underpinnings of PLC (Wilson, 1924). This theory is still the most influent in the field although not yet supported by definitive evidence. It postulates the existence of two cortical systems connected by the corticospinal tracts to a hypothetical brainstem "crying–laughing–facial–respiratory center" responsible for motor command of crying and laughter. The first system, located in the frontal lobes and in the motor cortex, exercises a volitional control, whereas the second, presumably integrated to the limbic system, processes the emotional valence of stimuli and causes laughing and crying to emerge involuntarily. According to this theory, the emergence of abnormal laughter and crying is due to an imbalance between the two systems and, for this reason, may manifest even after unilateral lesions.

For PLC the causal role of corticospinal tracts is strongly suggested by numerous case reports where the disorder manifested itself after uni- or bilateral strokes in the basis pontis (Mouton et al., 1994; Tei and Sakamoto, 1997). Furthermore several authors reported PLC as a presenting symptom of subtentorial tumors compressing the pons or the midbrain (Mouton et al., 1994; Tei and Sakamoto, 1997). In some of these cases PLC completely disappeared after surgical resection (Muzumdar et al., 2001; Muzumdar and Goel, 2003). The role of pontine structures is also suggested by the insurgence of the "fou rire prodromique" (an uncontrollable crisis of laughing that shortly anticipates a stroke) (Feré, 1903) before ischemic or hemorrhagic strokes generally located in the basis pontis (Wali, 1993). However, the role of other cortical and subcortical structures in the pathogenesis of laughing and crying is suggested by "gelastic" (laughing) and "dacrystic" (crying) epileptic crises in patients with hypothalamic hamartomas, by symptoms of patients with tumors or other lesions in the temporal or mesial frontal lobe (Arroyo et al., 1993; Dan and Boyd, 1998; Kahane et al., 2003; Pearce, 2004), and finally by the effect of the electrical stimulation in situ of several cortical (cingulate and basal temporal cortex) and subcortical (subthalamic nucleus) areas (Arroyo et al., 1993; Bejjani et al., 1999; Kahane et al., 2003; Okun et al., 2004; Pearce, 2004). In this context it is important to note that, in physiological conditions, the anterior cingulate cortex and hypothalamus are crucially involved in the generation of the autonomic components of emotions (Gainotti, 2001; Critchley, 2005). An alternative hypothesis based on a unique case report of a patient with multiple brainstem and cerebellar lesions (Parvizi et al., 2001) attributed to the cerebellum the role of adjusting laughter and crying according to the cognitive, emotional, and situational values of triggering stimuli. A specific linkage between EL and hemispheric stroke has not yet been demonstrated. Anterior cortical or left frontal lenticulocapsular lesions, particularly those involving the dorsal globus pallidus and temporal lobe, have been indicated as possible correlates in clinical studies that compared CT or MRI findings between groups of stroke patients respectively with and without EL (House et al., 1989; MacHale et al., 1998; Kim and Choi-Kwon, 2000). However these findings have to be considered with caution because of several methodological limitations (i.e., different criteria for PSE diagnosis). For patients with PSE it is still unknown whether the dysfunction is at the level of emotional processing or emotional regulation or, most likely, at both levels.

Functional neuroimaging studies in healthy individuals show that paradigms of sadness or happiness induction activate a great number of cortical regions. For sadness the correlations are more robust and consistent with the anterior cingulate cortex and insula (Phan et al., 2002). Although the anterior cingulate cortex and specific limbic areas such as amygdala and insula are only rarely and selectively damaged by ischemic stroke, their reciprocal projections to the frontal lobes, limbic striatum, and other paralimbic areas are very often involved in large strokes. However, given the central role of frontal–subcortical systems in emotional regulation (see further sections), it

is highly conceivable that the dysfunction of those systems is implicated in the loss of control of crying and laughing.

A neurochemical hypothesis posits that EL is the consequence of a dysfunction of serotoninergic neurotransmission. This hypothesis is supported by the abortive effect on crying and laughing disorders of SSRIs (Andersen et al., 1993; Nahas et al., 1998) and by the frequent involvement of the raphe nucleus (the main site of serotonin synthesis) and its efferences in cases of pontine, brainstem, and capsular strokes (Derex et al., 1997). The raphe nucleus in the brainstem gives rise to serotoninergic projections to the limbic forebrain, and serotoninergic receptors are widespread in the brain, especially in paralimbic areas (Feldman et al., 1997). This wide distribution of serotoninergic fibers and receptors makes them vulnerable to every kind of stroke. This could be a supplemental reason for the heterogeneity of lesion location attributed to EL.

From a psychological point of view, EL has been considered as one manifestation of a more general disorder of emotional control, assimilated, for example, to post-traumatic stress disorder. Stroke victims can live and remember the events of stroke as a trauma that severely disrupted their lives. From this perspective, the process of coping with the disease produces irritability, thoughts of reference, intrusive thoughts, and memories that could interfere with emotional regulation (Calvert et al., 1998). EL also causes distress, embarrassment, social avoidance, and impaired quality of social interaction. Furthermore, other people may perceive sudden crying or laughing as a sign of dementia or stupidity.

EL has been found as a risk factor for developing PSD within the first year after stroke onset (Carota et al., 2005) and both PSE and PSD favorably respond to SSRI drugs (Choi-Kwon et al., 2006). These findings suggest some pathogenetic mechanisms that are common to EL and PSD.

Response to SSRI does not appear to be the result of a simple antidepressant action because recovery also occurs in people without a depressive disorder and at times occurs in a dramatic fashion, within 24–48 hours after starting a low dose (Nahas et al., 1998). In a few cases, pharmacological treatment transformed crying into laughter (McCullagh and Feinstein, 2000).

31.3. Behavioral and personality changes

31.3.1. The frontal syndrome

The thesis suggesting that the frontal lobes are the main site of emotional and behavioral processing is based on several robust assumptions, either clinical or experimental. The prefrontal cortex, because of heavy bidirectional connections with all the other associative areas of the brain (with some specialization: the dorsal–lateral PFC with the dorsal stream and the ventral–lateral with the ventral visual stream), has long been assumed to have functions of control over other cognitive functions. This function has been termed executive (Tranel et al., 1994), meaning that rather than performing cognitive operations, such as memorizing, learning, and reasoning, the frontal regions are concerned with the deployment of such capabilities, which are carried out elsewhere in the brain.

Therefore, the role of the frontal lobes is regarded as "supervisory" (Shallice, 1988) or "managerial" (Grafman, 1989) rather than being limited to the performance of any specific cognitive function. The aim of executive functioning should be selecting and carrying out actions or behaviors throughout the complex integration and control of the activity of other associative areas (Milner, 1963; Luria, 1966; Baddeley, 1986; Shallice, 1988). The concept introduced by Baddeley (1986) assigns a crucial role to this central executive component and fMRI studies have consistently demonstrated that working memory tasks significantly activate the prefrontal areas (Ragland et al., 2002; Deco et al., 2004; Osaka et al., 2004; Narayanan et al., 2005).

Evidence of the role of the prefrontal cortex in behavior and personality changes comes from the description of patients with frontal lobe damage of several etiologies. Individuals with lesions in the prefrontal areas tend to be emotionally impulsive and poorly affectively regulated (Stuss and Benson, 1986; Kolb and Taylor, 1990; Damasio, 1994; Rolls et al., 1994; Tucker et al., 1995). Their behaviors include decreased concern with social propriety, environmental dependency, utilization, imitation and stereotyped behaviors, restlessness, exuberance, euphoria, facetiousness, extroversion, lack of restraint, purposelessness, childish behavior, distractibility, egocentricity, grandiosity, capriciousness and instability, social and sexual disinhibition, poor judgement, diminished foresight, social withdrawal, absence of tact, concreteness, acting on simple motivations, impulsiveness, self-centeredness, immorality, inertia, lack of ambition, indifference to the environment, satisfaction with inferior performance, slowness in thinking, bradypsychism, lack of emotional expression, decreased self-concern, shallow affect, depressed outwardly directed behavior and social sense, indifference, and alexythimia. Furthermore, several of these conditions may often occur together in the same patient (e.g., apathy reduced mental flexibility and euphoria), even in the absence of severe damage (Damasio, 1994). Stuss et al. (1992) suggested that the primary disorder for

all behavioral and emotional changes due to frontal system damage might be a personality disorder where lack of control and self-reflectiveness (vulnerability to interference, impoverished judgment, and inability to self-correct and self-monitor) are the key features. Hence, the DSM-IV taxonomy relative to personality disorders (paranoid, schizotypic, antisocial, borderline, histrionic, narcissistic, avoidant, and obsessive–compulsive) (DSM-IV, 2000) fits well with the so-called "frontal" behaviors. However, the reduction of such a vast array of clinical symptoms into the category of personality change still has poor operational value for researchers interested in developing neurobiological models of these disorders.

Hence, the precise nature of prefrontal regulatory mechanisms for emotion is mostly speculative. For example, it is not clear whether these mechanisms are specific to different impulses (e.g., emotional, appetitive, aversive) or to individual emotions. Researchers have yet to agree about even such basic issues as to whether the left or right prefrontal cortex is preferentially charged with the regulation of negative versus positive emotion (Dawson et al., 1992; Tucker et al., 1995). According to the classification of frontal–subcortical anatomofunctional systems (Alexander et al., 1986), three distinct prototypical behavioral syndromes of the frontal lobe have been proposed (Cummings, 1993; Mega and Cummings, 1994) (Fig. 31.1).

Thus, frontal lobe symptoms can be also related to stroke sparing the frontal cortex, such as caudate (Kumral et al., 1999), lenticulocapsular (Giroud et al., 1997) and thalamic strokes (Carrera and Bogousslavsky, 2006) or to inferior genu capsular infarction (Tatemichi et al., 1992; Schnider et al., 1996).

Patients with lesions of the dorsolateral frontal region (BA 8, 9, 10, 11, 43, 46, 47), following lobar hemorrhage or a watershed infarct, may manifest decreased drive, slowness in thinking, failure to recognize concepts and generate hypotheses, lack of flexibility, perseveration and stereotypical motor behavior (e.g., grasping), impulsive responding, acting on simple motivations, utilization and imitation behaviors (echopraxia), and (predominantly on the right side) response-to-next-patient stimulation (Bogousslavsky and Regli, 1988) and delusions/confabulations/misidentification syndromes. Possible associated deficits are reduced working memory; predominantly on the left side: transcortical motor aphasia, speech apraxia, agraphia, foreign accent syndrome, Broca's aphasia,

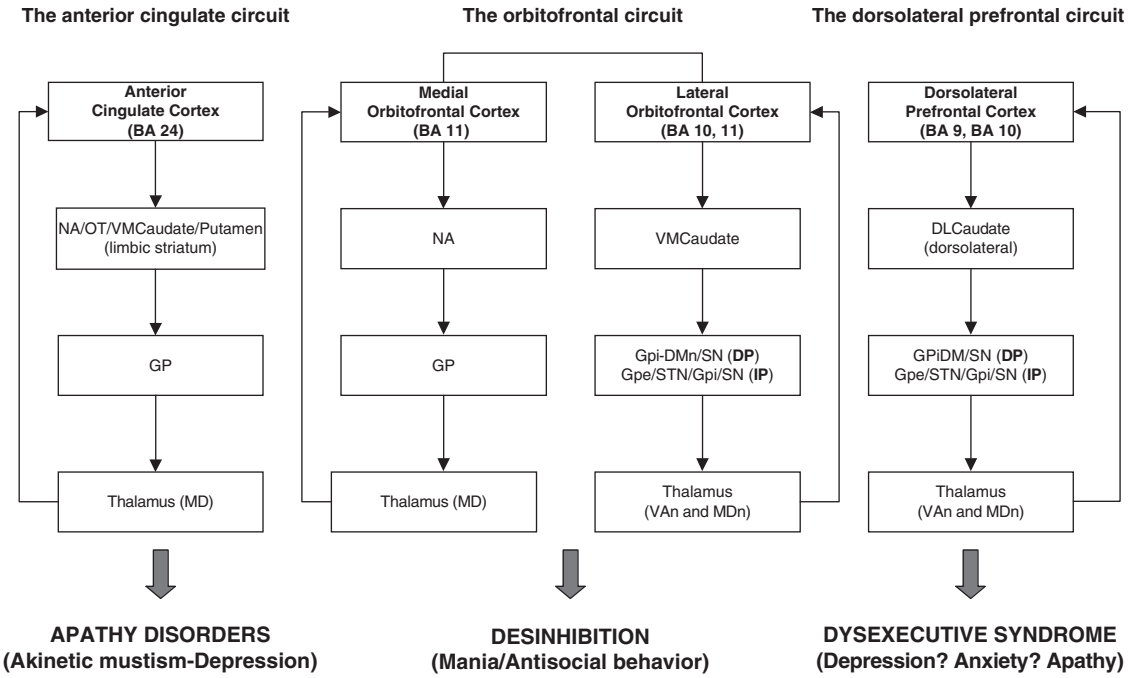

Fig. 31.1. Frontal-subcortical anatomofunctional systems and behavioral correlates, adapted from Mega, 1994. BA = Broadman area; NA = nuclear accumbens; VM = ventromedial; DL = dorsolateral; OT = olfactory tuberculum; GP = globus pallidum; GPi = globus pallidum internal; GPe = globus pallidum external; DP = direct pathway; IP = indirect pathway; DMn = dorsomedian nucleus; AVn = anterior ventral nucleus; SN = substantia nigra; STN = subthalamic nucleus.

global aphasia without hemiparesis, and limb-kinetic apraxia; predominantly on the right side: motor hemineglect (particularly directional hypokinesia), spatial neglect, constructive apraxia, motor impersistence and persistence (catalepsy-like), and eyelid-opening apraxia.

Frontomedial lesions, particularly in the area of the anterior cingulate cortex (BA 24) and the supplementary motor cortex (BA 6) tend to impair the ability to initiate behavior and result in amotivational or apathy syndromes. Lesions in the inferior frontomedial regions (subcallosal gyrus and mesial gyrus rectus) (BA 25,32,14,12) have been associated, besides apathy, with disinhibited behaviors. Associate deficits of frontomedial lesions might be utilization and imitation behavior, callosal disturbances, alien hand syndrome (Kikkert et al., 2006), intermanual conflicts (Suwanwela and Leelacheavasit, 2002), diagonistic dyspraxia, grasping (hand and foot), facial palsy with inverse automatic–voluntary dissociation, urination behavior (usually with large or bilateral involvement); on the left hemisphere: transcortical motor aphasia, buccolingual apraxia, ideomotor apraxia, and dyscalculia; on the right hemisphere: hypergraphia (Carota et al., 2003) and hemineglect.

Frontomedial lesions may result from occlusion of the anterior cerebral artery, mostly by embolism (Kumral et al., 2002), or from spasms after rupture of an anterior communicating artery aneurysm (Bogousslavsky and Regli, 1990). In the initial stage, patients may be entirely unable to initiate motor acts and communicate (akinetic mutism, abulia).

The orbitofrontal region (BA 10, 11, 13, 14, 47) is thought to mediate socially appropriate behaviors. Stroke circumscribed to this cortical region is rare except as a complication of rupture and repair of anterior communicating artery aneurysms. Lesions within the orbitofrontal system might produce marked personality changes such as impulsiveness, anger, irritability, explosiveness, tactlessness, affective ability, and lack of personal sensitivity, even in the absence of measurable cognitive deficits (Bechara et al., 1996; Bechara, 2004; Rolls, 2004).

Although focal lesions within frontal lobes are rare with stroke, frontal–subcortical systems and their heavy reciprocal connections with the limbic system (amygdala, hippocampal, and hypothalamic nuclei) and other cortical associative areas widely extend over the brain and are particularly vulnerable to every cortical or subcortical stroke. Thus, in the majority of cases, the ischemic lesion involves more than one system and patients usually present combined features of these syndromes.

Even though they were initially developed for patients with dementia or traumatic brain injury, the Neuropsychiatric Inventory (Cummings et al., 1994, 1997), the Neurobehavioral Rating Scale (NRS) (Levin et al., 1987), the NRS-revised (Levin and Mazaux, 1990), the Neuropsychology Behavior and Affect Profile (Nelson et al., 1994), the Frontal Systems Behavior Scale (FrSBe) (Stout et al., 2003) and the Frontal Lobe Personality Scale (FLOPS) (Grace and Malloy, 1992; Grace et al., 1999) are valid instruments, with high reliability and large-scale norms (Malloy and Grace, 2005), for screening in stroke patients a wide range of mood, affect, emotions, and behaviors related to frontal lobe dysfunction.

31.3.2. Anger, irritability, and aggressiveness

Anger is a basic emotion characterized by indignation, dislike, and belligerence and consists of cognitive (hostility) and behavioral components (verbal or motor aggressiveness, aggression). Irritability can be defined as being easily angered. Triggering stimuli may be variable and dependent on the context. Other non-stroke-related variables might be a factor, such as prior exposure to violence or alcohol and the presence of mood disorders. Therefore, anger is a complex and multicomponent phenomenon involving several developmental and sociocultural aspects. A commonly used and easily administered diagnostic instrument often used with stroke patients is the Spielberger Trait Anger Scale (Spielberger et al., 1983; Kim et al., 2002) (Table 31.3).

Irritability and aggressiveness are frequently observed in acute stroke in large cohorts (about 30–35% of patients with first-ever stroke), without any clear clinical and neuroimaging correlates (Aybek et al., 2005; Santos, 2006). However, in a sample of 18 patients with acute stroke, younger age, depressive symptoms, cognitive impairment, and localization of the lesion over the anterior regions of the left hemisphere were considered risk factors (Paradiso et al., 1996). In another study (Angelelli et al., 2004) irritability was found to be associated with left hemisphere lesions and aphasia. In this study, in rehabilitation settings, several months after stroke onset, irritability was mostly characterized by impatience with little things like waiting and less frequently by flashes of anger, rapid mood changes, and quarreling. In another study, 3 or 12 months post-stroke, inability to control anger and aggression was found to be associated with motor dysfunction, dysarthria, emotionalism and frontal–lenticulocapsular–pontine areas (Kim et al., 2002).

In previous sections, we described the catastrophic reaction, a behavior that shares similarity with the

Table 31.3

The 10-item Spielberger Trait Anger Scale

1. I am quick-tempered
2. I have a fiery temper
3. I am a hotheaded person
4. I get angry when I am slowed down by others' mistakes
5. I feel annoyed when I am not given recognition for doing good work
6. I fly off the handle
7. When I get angry, I say nasty things
8. It makes me furious when I am criticized in front of others
9. When I get frustrated, I feel like hitting someone
10. I feel infuriated when I do a good job and get a poor evaluation

episodic dyscontrol syndrome (Eames and Wood, 2003). Indeed, both conditions are characterized by a strong component of anger and aggressiveness. A personality trait consisting of being prone to anger or anger expression has also been associated with an increased risk of stroke and myocardial infarction (Williams et al., 2002; Eng et al., 2003).

Concerning possible therapies, a line of approach consists of cognitive and behavioral methods, in which patients have to recognize initial symptoms of aggression, as well as relaxation methods. However pharmacological therapies are more often necessary to control such symptoms in patients with brain damage. They include beta-blockers, neurolepticsm, or buspirone. Carbamazepine may also have valuable effects (Azouvi et al., 1999).

31.3.3. Apathy

Apathy is defined as a lack of goal-directed activities due to reduced motivation (Marin, 1991). In order to make such a diagnosis, one should be certain that the symptom, of which the severity may be extremely variable after stroke, constitutes a significant change from the subject's baseline personality and that it has significant consequences on daily living activities. Apathy has behavioral, cognitive, and emotional components.

The cognitive dimension is related to loss of motivation or interest in engaging in activities and the emotional dimension corresponds to emotional flattening and decreased emotional experience. This type of emotional flattening seems to be associated with impaired autonomic responses to the emotional valence of stimuli (Annoni et al., 2003). Behavioral correlates of apathy are the reduction of the verbal spontaneity (long latencies, short sentences, or even monosyllabic responses, verbal perseverance, motor and mixed transcortical aphasia) and motor inertia (including slurred speech and hypophonia for verbal motor acts)

The Apathy Evaluation Scale (Marin et al., 1991), and the Apathy Inventory (Robert et al., 2002) are useful instruments to assess behavioral, cognitive, and emotional components of apathy and their severity. Clinical studies that adopted standardized questionnaires of apathy suggest a prevalence of 20–50% in the first months after stroke (Starkstein et al., 1993a; Okada et al., 1997; Brodaty et al., 2005). However, these scales, if used in isolated manner, do not always differentiate apathy from depression (Levy et al., 1998).

Unlike depression, apathy dose not produce subjective distress (sadness, tearfulness, anxiety, recurrent thoughts of disease and death) and negative bias in response to emotional stimuli (Andersson et al., 1999). The possibility of dissociating apathy from depression has been confirmed in studies on stroke patients (Marin et al., 1994). Stroke-related apathy usually manifests with other behavioral and cognitive features of a dysexecutive syndrome (reduced mental flexibility, psychomotor speed, and automatic control) and with the emergence of archaic reflexes. However in some cases, when supplemental time is not allowed to patients, apathy could contribute to the perception that patients are more cognitively impaired than they actually are.

Abulia and akinetic mutism are extreme disorders of apathy. Patients with these conditions appear awake and their eyes can follow the examiner but they may be entirely unable to initiate motor acts and communicate, may be incontinent, eat and drink only when fed, speak in monosyllables, if at all, and display no emotion even in the face of pain. Abulia and akinetic mutism occur from bilateral stroke of the frontal lobe including the cingulate cortex, orbital gyri and septal areas, mesial motor areas, and subcortical regions such as the caudate, putamen, and thalamus (Nagaratnam et al., 2004).

All the clinical studies investigating apathy suggest the role of a dysfunction within fronto-subcortical circuitries (dorsolateral prefrontal region, cingulate gyrus, supplementary motor area, basal ganglia, and dorsomedian thalamic nucleus) and small lesions of the paramedian reticular formation in the diencephalons and midbrain. These regions have heavy connections with limbic and paralimbic areas. Studies of regional blood flow in stroke patients with high apathy scores showed hypoactivity in dorsolateral frontal and temporofrontal regions (Okada et al., 1997).

Ischemic or hemorrhagic acute strokes involving the thalamus, especially in cases of bilateral lesions, may manifest with apathy together with significant memory and attention deficits, and relevant signs ("palypsychism," verbal perseverations) of a dysexecutive syndrome (Chatterjee et al., 1997; Ghika-Schmid and Bogousslavsky, 2000). Thalamic limbic nuclei (ventral anterior [VA] nucleus and medial dorsal [DM] nucleus) are relay nuclei in both the dorsolateral frontal and the anterior cingulate frontal–subcortical functional systems. Apathy occurring with disinhibition is also reported as a consequence of thalamic (Fukutake et al., 2002) or caudate stroke (Bhatia and Marsden, 1994).

In acute stroke, high levels of apathy also occur in patients with extended ischemic lesions in the right middle cerebral artery territory. These patients present diminished levels of vigilance or sustained and spatial attention, respond less to facial expression, body language and prosodic aspects of speech, and show emotional indifference. Patients with right-sided lesions show an inverse correlation of apathy scores with heart rate reactivity (Bhatia and Marsden, 1994). Apathy emerging after right-sided lesions suggests that apathy, emotional indifference, and anosognosia are related phenomena and highlight the dominant role that the right hemisphere generally has in both attentional and emotional processes.

Clinical, pharmacological, and experimental studies indicate that the catecholaminergic systems, particularly the mesolimbic dopaminergic system, are the key modulators of motivated behaviors (McAllister, 2000). The dopaminergic agonists, particularly bromocriptin (5–20 mg/day) and amantadin are helpful in treating apathy but blind placebo-controlled studies are needed to guide pharmacological interventions.

31.3.4. Athymormia

Athymormia or loss of psychic autoactivation indicates an overt reduction of motivated behaviors reversible with external stimulation (Laplane et al., 1984; Laplane and Dubois, 2001). Patients with athymormia manifest apathy, aspontaneity, and indifference, generally without suffering, anxiety, or depression.

The affective indifference of athymormic patients is quite evident, even for life events that could be remarkable. They have no internal resources necessary to initiate even minor activity. This disorder corresponds primarily to a mental void that, differing from patients with abulia, does not associate with bradypsychism or executive dysfunction and that reverses with stimulation by another person. Patients engaging successfully in complex activities after repeated stimulation is a sign of dissociation between a deficit of autoactivation and an intact heteroactivation.

Cases reported in the literature are due to bilateral lesions of the basal ganglia (Habib, 2000) and thalamus (Bogousslavsky et al., 1991). This syndrome could result from a frontostriatal–limbic disconnection that manifests with reduced motivation to act and to process emotions but that notably spares cognitive and motor functions (Habib, 2000).

31.3.5. Obsessive–compulsive disorder

Obsessive–compulsive disorder (OCD) is defined by the presence of intrusive thoughts, preoccupations, or obsessions that generate rituals or stereotyped or aberrant motor behaviors. These compulsive behaviors are often different from the preservative behaviors of patients with acute frontal lesions. Patients with OCD have insight into the pathological nature of their condition but feel increasing anxiety when they attempt to inhibit compulsive acts.

This condition is rare after stroke. Few cases of OCD have been reported with stroke and almost all involved basal ganglia lesions (Paunovic, 1984; Laplane et al., 1989; Daniele et al., 1997; Carmin et al., 2002). OCD occurred after a period varying from days to years after stroke, often with progressive worsening over time. Based on these cases, it has been postulated that basal ganglia, particularly the caudate nucleus and the mediodorsal thalamic nucleus, exert a regulatory control on the orbitofrontal cortex where obsessive–compulsive behaviors could be generated (Etcharry-Bouyx and Dubas, 2000). Treatment of post-stroke OCD includes medication, but cognitive-behavior therapy—in the form of exposure and response prevention—also seems to be potentially effective (Carmin et al., 2002).

31.3.6. Sexual changes

Hyposexuality is a decrease in libido and sexual drive, manifesting with impotence or a decline in erotic thinking and discourse. Sexual dysfunction is frequent after stroke and correlates with lesions of the left hemisphere and the presence of depression or emotionalism (Kimura et al., 2001; Choi-Kwon and Kim, 2002). Sexual dysfunction (both in men and women) may be associated either with stroke co-morbidities (as diabetes or chronic heart failure) or psychological factors such as fear of impotence, inability to discuss sexuality, unwillingness to participate in sexual activity, and the degree of functional disability (Korpelainen et al., 1999).

Hypersexuality is less frequent than hyposexuality and manifests with inappropriate social behaviors

(such as masturbation), or verbal comments with explicit or implicit sexual connotation (Spinella, 2004). A change of sexual orientation (e.g., heterosexual into homosexual) after minor thalamic and temporal stroke has been reported (Cheasty et al., 2002).

Aberrant sexual behavior (increased autoerotic, homosexual, or heterosexual activities, or inappropriate sexual object choice) is one symptom of Klüver–Bucy syndrome (KBS), the others being passiveness with loss of fear or anxiety, dietary changes (bulimia and loss of alimentary selectivity), hypermetamorphosis (excessive visual exploration of environment), hyperorality (tendency to examine all objects by mouth), "psychic blindness" (failure in recognizing emotional visual stimuli). Patients with KBS generally have also severe cognitive deficits such as amnesia, loss of semantic knowledge, aphasia, and visual or multimodal agnosia.

Hypersexuality or KBS in the stroke literature has been reported with thalamic (Muller et al., 1999; Cheasty et al., 2002; Spinella, 2004) and subthalamic lesions (Absher et al., 2000). The putative mechanism is the dysregulation of limbic areas (probably amygdala) involved in thalamic loops.

31.4. Cognitive and behavioral disintegration

31.4.1. Acute confusional state and delirium

Patients with acute confusional state lose their customary speed, clarity, and coherence in thinking. This phenomenology suggests that the disintegration of cognitive and emotional process is due to severe depletion of attention resources. The symptoms develop during short period, fluctuate during the day, and cannot be explained by pre-existing dementia. Attention and concentration resources are poorly available: the patient is unable to register and recall events, spatiotemporal coordinates are lost, irrelevant thoughts can intrude, and language may be impaired (anomia and incoherent speech), generally in the absence of aphasic signs (e.g., paraphasias) that could point to specific regional brain dysfunction. Patients show daytime sleepiness, nocturnal agitation, and fragmented sleep or insomnia. Delirium reproduces the same symptoms but is characterized by increased psychomotor and vegetative activity, by a severe perception disorder (vivid dreams and hallucinations), by intense emotional changes, and by a tendency to convulse.

Stroke without lateralizing signs such as sensorimotor deficits or cognitive dysfunction (aphasia or unilateral spatial neglect) is a relatively infrequent cause of acute confusional state and delirium (Ferro et al., 2002). Thus, stroke should be considered as an exceptional diagnosis of a pure confusional state.

Strategic lesions involve, usually on the right hemisphere, the territory of the middle cerebral artery, frontal or temporoparieto-occipital regions (Price and Mesulam, 1985; Dunne et al., 1986; Mori and Yamadori, 1987; Cummings, 1992; Henon et al., 1999), or the territory of the posterior cerebral artery (unilateral [preferentially left] or bilateral lesions) (Medina et al., 1974; Caplan, 1980; Devinsky et al., 1988). Cases have been reported with bilateral or unilateral (right or left) caudate nucleus infarction (anterior cerebral artery (ACA) or middle cerebral artery (MCA) territory) (Mendez et al., 1989; Caplan et al., 1990) with bilateral or unilateral (right more than left) thalamic stroke (Graff-Radford et al., 1984) and with capsular genu infarction (thalamocortical disconnection) (Tatemichi et al., 1992). In the left hemisphere confusional states can manifest with posterior strokes within the MCA, usually in association with aphasia or with temporal infarction in the PCA territory and generally with severe memory disturbances (Devinsky et al., 1988).

The preferential stroke localization in the right hemisphere for acute confusional state or delirium with altered sensorium suggests its dominant role in the management of attentional resources and for perceptive processing. Following stroke, hallucinatory experiences probably reflect the abnormal activation of associative areas of the parietotemporo-occipital junction that are neighboring to the lesion, which subtend polymodal integration of stimuli. However, the occurrence of a confusional state following stroke can be also related to other factors such as advanced age, the concomitance with pre-existing dementia or cognitive impairment, and the presence of cerebral atrophy (Henon et al., 1999) or leucoencephalopathy.

31.5. Perception-identity disorders

31.5.1. The self: anosognosia of hemiplegia/ somatoparaphrenia

Anosognosia of hemiplegia (AHP) consists of hemiplegia negation of the limb or limbs contralateral to the stroke side. In clinical studies, Bisiach's criteria (Bisiach et al., 1986) are generally used to establish diagnosis of AHP but other questionnaires can be helpful tools in systematic investigation of this disorder (Nathanson et al., 1952; Berti et al., 1996).

However, according to some authors (Baier and Karnath, 2005), the minimal requirement for retaining the existence of this syndrome in a given patient should be the repeated negation of hemiparesis on verbal questioning. The non-acknowledgement of the hemiparesis despite irrefutable demonstration in motor

tasks corresponds to a further degree in severity. However, the Bisiach's criteria do not take sufficiently into account the incredible variety of clinical phenomena related to this syndrome. This variety of signs related to AHP is amplified by the fact that they can fluctuate in time and also depend on the examiner's creativity and ductility in questioning the patient.

Hence, in less severe cases the patients can recognize limb paralysis, but show a curious indifference or some degree of euphoria at its regard (anosodiaphoria). The patient may not only deny the paralysis but could affirm, against all evidence, that the paralyzed limb is moving (illusory limb movements). He can also deny the ownership of the paralyzed limb (somatoapraphrenia) attributing it to other persons (generally the spouse or other family members), or consider the limb as inhuman. In extreme cases the patient can deny the existence of the limb (asomatognosia), but it should be checked that he is not using metaphoric expressions. Rarely patients can report limb reduplication or multiplication. Less frequently the patients feel threatened and ask to move the limb away or insult it (misoplegia). These absurd behaviors and beliefs often contrast with the relative integrity of other cognitive faculties and are generally reported with indifference. In these cases the distorted conscience of the body and reality in general strongly refers back to thought disturbances that are typical of schizotypic disorders.

Some patients recognize, on the left body, the paralysis of only one limb when both limbs are paralyzed; others can admit the paralysis but insist in attributing it to other pathologies (flu-like disease, arthrose, heart disease). Dissociation between the acknowledgement of the deficit and its consequence is also possible (Marcel et al., 2004). For instance the patient's behavior can be both congruent with the anosognosia (he will try to walk and quit the hospital), and incongruent (he mysteriously accepts staying in a wheelchair). In this last situation some or implicit acknowledgment of the paralysis should exist. The absurd explications and false beliefs that patients report on their paralyzed limb constitute confabulations. The confabulation can be considered, in general terms, as a genuine false belief (Berlyne, 1972). Similarly patients with anosognosia of hemianopia (AHO) do not complain of lateralized visual problems even though they see only part of objects, faces, and written words.

AHP and AHO generally coexist and associate with unilateral spatial neglect (USN) although double dissociations have been described (Jehkonen et al., 2000a). AHP is a syndrome of the acute phase of stroke because it rapidly improves, generally more than unilateral spatial neglect (Jehkonen et al., 2000b); therefore its role for long-term functional recovery is debated (Jehkonen et al., 2001). Persistence of severe AHP for longer than 1 month is rare (Cocchini et al., 2002; Venneri and Shanks, 2004).

AHP and AHO are syndromes of the right hemisphere. This is confirmed by studies showing that, after left carotid amytal injection, their frequency is undoubtedly higher than in case of right carotid injection, even if aphasia could contribute to underestimate AHP to a certain degree (Breier et al., 1995; Meador et al., 2000).

AHP and AHO are related to almost overlapping stroke locations in the middle cerebral artery territory, generally the posterior parietal lobe. However, AHP is observed less frequently than AHO after stroke in the PCA territory or in the occipital lobe (Celesia et al., 1997; Pia et al., 2004). AHP can also manifest in the right hemisphere as a result of frontal and subcortical lesions (Pia et al., 2004), or thalamus (Karussis et al., 2000) or capsulo-lenticular (de la Sayette et al., 1995) strokes. Rare cases are reported with lesions in the brainstem, pons (Evyapan and Kumral, 1999) and midbrain (Bakchine et al., 1997). In these cases diaschisis is probably the causal mechanism.

The different phenomena related to AHP suggest that different mechanisms may be implicated. They are spatial and motor unilateral neglect (Vallar et al., 2003; Vuilleumier, 2004); the general diminution of attentional resources combined with the loss of proprioceptive afferences (which prevents paralysis discovery) (Levine et al., 1991); a body schema dysfunction (Head and Homes, 1911) or self-awareness; damaged spatial imagery; distorted adaptation of spatial egocentric frames and proprioceptive afferences to ongoing movements; loss of expectancy of movement or absence of implicit intention to move (Gold et al., 1994; Heilman et al., 1998); and finally the failure of the system that monitors the state of the body (Kaplan et al., 1993; Knight and Grabowecky, 1995; Venneri and Shanks, 2004).

However, although these different theories are founded on valid observations, most of them preferentially account for limited aspects of the syndrome rather than referring to a central mechanism (Jehkonen et al., 2000a; Marcel et al., 2004). For instance, transitory improvement of AHP with caloric vestibular stimulation suggests the role of distorted spatial body frames (Cappa et al., 1987; Vuilleumier, 2004) but does not explain the nature of confabulations. Thus the multifaceted nature of AHP has to be acknowledged, just as, after lesions of the left hemisphere, aphasia is known to include a wide variety of syndromes.

In fact, there is not yet a theory that sufficiently explains the association of AHP with right hemisphere

damage. Several results seem to refuse the hypothesis of an interhemisphere disconnection (Geschwind, 1965; Loring et al., 1989); for example, the presentation and manipulation of the paretic limb in the right visual field (directly perceived by the left hemisphere) does not modify the syndrome (Adair et al., 1997). Confabulations could not be the result of an incorrect verbal processing of the left hemisphere disconnected from the right because patients with AHP show further nonverbal failure in recognizing the paralysis (they try to walk or they attempt bimanual tasks such as applauding) (Ramachandran, 1995).

The role of psychological mechanisms such as coping with a reality that may be inadmissible to the patient (Weinstein and Kahn, 1950) has been revised. For instance, psychological mechanisms just do not explain the preferential association of AHP with right hemisphere damage. It would be difficult to admit a psychological defense for only a left and not for a right hemiplegia. The role of a general cognitive deterioration or a memory deficit is difficult to sustain because several patients with AHP are not impaired regarding such aspects (Marcel et al., 2004).

In conclusion, the variety of both stroke location (mainly frontal, temporal, and parietal lobe and thalamus) and clinical symptoms and signs of AHP suggest the role of multiple mechanisms controlled by a neural system (or a matrix) that is diffuse and for which the right hemisphere is dominant. It is important to note that this system, in physiological conditions, has to contribute to a certain degree to the awareness of the self.

31.6. Other people and places: misidentification syndromes

In even more rare circumstances with stroke, the failure is not in processing the status of one's own body but in perceiving or identifying certain elements of the external world. It would be more correct to indicate the following conditions as disorders of identity processing of people, places, and objects. It is important to note that this occurrence is more probable with psychiatric disorders (psychosis or schizophrenia) without brain damage, than after stroke. Therefore such syndromes are definitively located at the interface between neurology and psychiatry.

Capgras syndrome and reduplicative paramnesia are the most frequent of the misidentification syndromes. The patient with Capgras syndrome (Capgras and Reboul-Lachaux, 1923) is convinced that impostors, counterparts, aliens, or robots have replaced one or several intimate persons and feel in danger. The attribution of a false identity may also concern inanimate objects (Ellis, 1996), voices (Reid, 1993; Lewis, 2001), and domestic animals (Anderson, 1988). Surprisingly the patient may manifest reduced interest for what has happened to the original person after his substitution.

In the case of the reduplicative paramnesia (Pick, 1903), the patient is firmly convinced that he is in a different place despite any concrete evidence to the contrary. It could be a reduplication of places (e.g., he believes in the existence of two identical places with the same name but geographically separated), the chimerical assimilation between his house and the hospital (e.g., the house has been transformed into the hospital), or other aberrant ideas (e.g., he is elsewhere in another familial place). With the syndrome of "subjective doubles" (Christodoulou, 1978) the patient believes that someone else has replaced him. The Fregoli syndrome (Courbon and Fail, 1927) corresponds to a sort of hyperidentification. The patient with this disorder believes that strangers are actually known persons who are disguised in order to persecute him. A similar syndrome is the intermetamorphosis (Courbon and Tusque, 1932), where the patient believes that people reciprocally exchange their identities.

For these syndromes the amalgam between real and delirious elements may be variable. Occasionally we see patients hiding their beliefs for fear of not being credible; however, more often, they can react, even aggressively, to their delirium. The duration of this syndrome is generally limited to the acute phase of stroke but chronic cases have been reported (Vighetto et al., 1980). The association with damage to the right hemisphere largely prevails, although generally is settled in the context of diffuse cortical atrophy or bilateral frontal dysfunction (Forstl et al., 1991; Fleminger and Burns, 1993).

Reduplicative paramnesia has been reported with right frontal, parietal, temporal and thalamic stroke (Feinberg and Shapiro, 1989; Hudson and Grace, 2000) and Capgras syndrome with right frontal (Signer, 1994) and parieto-occipital stroke locations (Ellis, 1994). The mechanisms emanating from these syndromes remain uncertain. Attention, memory, visuospatial deficits and topographical disorientation can be concomitant but do not entirely account for the false beliefs of reduplicative paramnesia.

Capgras syndrome has been interpreted in the context of a model of face recognition constituted by two pathways (Ellis and Young, 1990). The first is determinant for the identification of the face and the second for triggering the affective response, which is usually associated to that face. Failure of the first pathway engenders prosopagnosia; the damage of the second pathway generates an identity/affective incongruence.

The evidence that psychiatric patients with Capgras syndrome, compared with patients with prosopagnosia (Bauer, 1984), do not show normal skin conductance responses to famous faces (Ellis et al., 1997) supports this theory. Even if these data should be corroborated by further studies on larger samples of patients by using stimuli controlled for familiarity and affective valence, they allow the hypothesis of a novel model of face recognition (Breen et al., 2000).

Regarding anatomoclinical correlations, there are sufficient clinical and experimental data supporting the idea that the fusiform gyrus of the right temporal lobe is determinant for face recognition (the first pathway). However, brain regions involved in emotional recognition of faces remain uncertain. They could be located on a dorsal system (parieto-occipital junction, inferior parietal lobule, superior temporal sulcus, cingular gyrus, amygdala) or on a ventral system, located in the temporal lobe, which parallels circuitries of the face recognition system. Similarly to Capgras syndrome, reduplicative paramnesia could result from a disconnection of brain areas involved in place recognition (hippocampal and parahippocampal gyrus) from areas involved in emotional processing of familiar places (Hudson and Grace, 2000).

A complementary hypothesis conceives that working memory dysfunction secondary to right frontal damage may be responsible for difficulty in negotiating simultaneously cognitive and emotional data relative to an identity (Papageorgiou et al., 2002, 2003). The disconnection hypothesis (Joseph, 1986) supposes that misidentification syndromes derive from a disturbed integration of the two hemispheres as each hemisphere may have a different role in processing identities. Another theory conceives a disconnection from frontal areas implicated in self/other discrimination and a parietotemporal or occipitotemporal region involved in sensorial analysis of identity features (Sellal et al., 1996). This theory gives relevance to feelings of alienation, depersonalization or unreality that are manifest with misidentification syndrome, either with neurological or psychiatric disorders (Christodoulou, 1978; Feinberg and Shapiro, 1989), and that resemble "déjà vu" or other similar phenomena of temporal lobe epilepsy. The role of dopaminergic transmission should be the object of further investigations because misidentification syndromes respond to neuroleptic drugs. Research on these disorders can bring novel insights into the neurobiology of paranoid schizophrenia.

31.7. Spontaneous confabulations

As in the case of anosognosia and misidentification syndromes, false beliefs or confabulations permeate the conversation of patients with this syndrome, which occurs after bilateral ischemic or hemorrhagic stroke of the median orbitofrontal region, generally after the rupture of an anterior communicating artery aneurysm.

The behavior of these patients is guided by memory traces that are founded in reality but that do no longer belong to the ongoing reality (Schnider, 2001). For example these patients may want to quit the hospital to return to professions that they left many years previously. This syndrome is generally associated with an amnesic syndrome or with a severe memory disturbance. However, in contrast to other amnesic disorders, where confabulations seem to replace memory voids, patients with spontaneous confabulations deeply believe their version of reality and act consequently with regard to behaviors and emotional responses. This rare syndrome suggests that in physiological conditions the perception of the ongoing reality depends, at least partially, on an unconscious capacity to inhibit the emergence of unwanted or non-pertinent memory traces.

31.8. Conclusion

The psychopathology of stroke remains a field accessible to clinical and experimental research. One of the major interests in such research is the attempt to isolate neurobiological factors implicated in the emergence of psychiatric symptoms in patients who do not show structural signs of brain damage. It is an area that requires multidisciplinarity. For this reason it is important to adopt specific and operational diagnostic criteria and to use a common language among clinicians and researchers. The relevance is also due to the high prevalence of behavioral and mood changes in the recovery phases of stroke, especially in elderly patients. Neuropsychiatric symptoms aggravate cognitive and sensorimotor deficits and can seriously interfere with rehabilitation programs and social reintegration.

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Chapter 32

Vascular dementia

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32.1. History of vascular dementia

The knowledge and the comprehension of dementia related to cerebrovascular diseases has greatly improved since the first descriptions at the end of the nineteenth century. The classical descriptions of Alzheimer (Alzheimer, 1895) and Binswanger (Binswanger, 1894) distinguished different forms of vascular dementia: subcortical chronic progressive vascular encephalopathy (Binswanger's disease), arteriosclerotic cerebral atrophy, dementia apoplectica, and perivascular gliosis. Cerebrovascular disease was viewed as the preponderant cause of dementia in the early twentieth century (arteriosclerotic dementia). In the 1960s, Alzheimer's disease became known as the commonest etiology of dementia with cerebral arteriosclerosis a rare entity. In the 1970s, Tomlinson et al. (1970) established a link between the cerebral volume lesions and dementia, advancing that a loss of more than 100 ml of cerebral tissue was necessary for dementia to occur. Hachinski et al. (1974) introduced the term "multi-infarct dementia," proposing that cognitive dysfunction depends not only on the size, but also the localization and the number of the ischemic lesions. At the end of the twentieth century, vascular dementia was recognized as the second predominant cause of dementia after Alzheimer's disease. The concept of vascular dementia enlarged (Roman et al., 1993), including dementia due to multiple infarcts, strategic infarcts, small-vessel disease, cerebral hypoperfusion, and hemorrhage. The concept received a further degree of complexity by the awareness that vascular dementia can also occur without any clinical stroke (no-stroke dementia) (Emery et al., 2005). Recently the relationship between vascular dementia and Alzheimer's disease has appeared more complex. The two entities often occur simultaneously and share some identical pathogenic mechanisms (Kalaria, 2002). It is maybe no longer the question of how to distinguish vascular dementia and Alzheimer's disease, but rather of how vascular and Alzheimer's disease lesions interact and contribute to dementia.

32.2. Epidemiology of vascular dementia

The precise epidemiology of vascular dementia is difficult to determine, because of the methodological differences between studies and the lack of consensus on diagnostic criteria. Neuropathological examinations offer an important way to assess precisely the various types of dementia. According to the criteria set by the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et L'Enseignement en Neurosciences (NINDS-AIREN) (Roman et al., 1993), a "definite" diagnosis of vascular dementia should be made by clinical examination, completed by neuropathologic evidence of cerebrovascular disease and in the absence of Alzheimer's disease lesions. While the final diagnosis of Alzheimer's disease can only be made by autopsy, no validated neuropathologic criteria exist for vascular dementia, because of the large variability of its pathogenesis.

Most studies rank vascular dementia as the second leading cause of dementia after Alzheimer's disease (Jorm, 1991). Recently, it has been raised that a mixed vascular and degenerative dementia may be the most frequent form of dementia (Korczyn, 2002). Cerebrovascular disease is common in the elderly and histologic

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lesions of Alzheimer's disease often coexist with vascular pathologic changes (Galasko et al., 1994). Moreover, cerebral infarction can strongly aggravate the clinical expression of Alzheimer's disease (Snowdon et al., 2002). With progressive aging of the population, vascular dementia might become the first etiology of all dementias (Roman, 2002b).

The percentage of vascular dementia of all cases of other dementias varies across studies. A collaborative study conducted in Europe reported that vascular dementia represents 15–20% of all dementia and Alzheimer's disease between 60–70% (Fratiglioni et al., 2000; Lobo et al., 2000). Ethnic variation exists, with less frequent vascular dementia in Western countries than in Asia, where vascular dementia could account for about 50% of all cases of dementia (Jorm et al., 1987; Jorm, 1991; Shaji et al., 2005; Zhang et al., 2005), likely related to high stroke rates and environmental differences. The prevalence of vascular dementia, according to a meta-analysis of international studies (Jorm et al., 1987), ranges from 1.5% in the 70–75-year-old population, to 15% in the population above 80 years old. Due to methodological differences, incidence varies a lot among studies (Jorm and Jolley, 1998), ranging from 0.3 to 12 persons per 1,000 per year in individuals older than 65 years old (Dubois and Herbert, 2001). The prevalence and incidence of vascular dementia increase exponentially with age (Rocca et al., 1991; Jorm and Jolley, 1998; Lobo et al., 2000) and, in contrast to Alzheimer's disease, are generally higher in men (Jorm et al., 1987; Rocca et al., 1991; Ruitenberg et al., 2001). Women tend to have a higher incidence of Alzheimer's disease in old age and men of vascular dementia in a younger age (Jorm and Jolley, 1998).

The most common form of presentation among the different clinical vascular dementia subtypes is post-stroke dementia. Approximately one-quarter of individuals older than 60 years old present with dementia 3 months after a stroke (Tatemichi et al., 1990, 1993; Desmond et al., 2000). Ischemic strokes also increase the long-term risk of having dementia. In an aged population, individuals with stroke have a five-fold (Tatemichi et al., 1994) to nine-fold (Kokmen E et al., 1996) risk of dementia versus non-stroke individuals at 4 years follow-up. Still, the true frequency of dementia after stroke is probably underestimated. Because of the high morbidity and mortality of strokes, many individuals are not available for a follow-up assessment (Desmond et al., 1998). Patients with aphasia are usually not diagnosed as having vascular dementia because their cognitive status is difficult to evaluate. Aphasia is probably often associated with vascular dementia (Censori et al., 1996).

The prognosis for patients with vascular dementia is worse than for patients with Alzheimer's disease. The 3-year mortality rate over the age of 85 years old is 67% in vascular dementia, compared to 42% in Alzheimer's disease and 23% in non-demented individuals (Skoog et al., 1993). One study (Fitzpatrick et al., 2005) estimated the survival from dementia onset was about 3.9 years for vascular dementia, 7.1 years for Alzheimer's disease and 5.4 years for mixed dementia, compared to 11 years for age-matched controls. Vascular dementia patients mostly died from cardiovascular disease. The cost and financial impact appear to be higher for vascular dementia than Alzheimer's disease (Sicras et al., 2005).

32.3. Risk factors and mechanisms

By definition, the diagnosis of vascular dementia is associated with cerebrovascular disease. Therefore, risk factors for vascular dementia have been described as being the same for stroke (Gorelick et al., 1993). Risk factors for vascular dementia (Tatemichi et al., 1993; Skoog, 1998) (Table 32.1) include advanced age, male sex and ethnicity, family history, and body weight (Stewart et al., 2005). A lower level of education has been linked to vascular dementia, possibly reflecting a diminished functional brain reserve (Tatemichi et al., 1994). The implication of an ischemic process is necessary for vascular dementia to occur, either via an occlusive, hypoxic, or hypoperfusive mechanism. Vascular factors include (Table 32.1) hyperlipidemia, diabetes mellitus, cigarette smoking, stroke, hypertension, orthostatic hypotension (Guo et al., 1996), hypoperfusion (Passant et al., 1996, 1997), cardiac disease, atrial fibrillation, white matter lesions,

Table 32.1

Risk factors for vascular dementia

Non-vascular factors	Vascular factors
Increasing age	Prior strokes (particularly if large, multiple or in vulnerable locations)
Male sex	White matter lesions
Ethnicity (e.g., Asian)	Hypertension
Low education level	Hyperlipidemia
Genetic predisposition (e.g., CADASIL)	Diabetes mellitus
	Cigarette smoking
	Cardiac disease
	Atrial fibrillation
	Hyperhomocysteinemia
	Hypoperfusion

hyperhomocysteinemia, and the e4 allele polymorphism of the apolipoprotein E genotype (APOE-e4) (Slooter et al., 2004).

32.3.1. Stroke

Stroke increases the risk of vascular dementia (Tatemichi et al., 1994), but not all patients with stroke will develop it. Specific patient and stroke characteristics could determine the occurrence of dementia after stroke (Tatemichi et al., 1993). Stroke-related factors have been identified such as: volume of cerebral tissue loss; infarct number; location, left-sided hemispheric rather than sub-tentorial lesions; and subtype infarction, such as lacunar infarcts and concomitant cerebral atrophy. The three most common mechanisms are multiple cortical infarcts, subcortical small-vessel disease, and strategically located infarcts. Silent ischemic events also play a role in the occurrence of vascular dementia.

32.3.2. Chronic hypertension

Hypertension is associated with several pathologies, which may lead to cerebral infarction and cognitive deficits. Patients with hypertension before stroke show more cognitive difficulties 3 months after stroke than those without (Rowan et al., 2005). Hypertension is associated with arteriosclerosis and may cause arterial and small-vessel lesions. Above and below a certain range, blood pressure may break down cerebral blood flow autoregulation. Reduction of blood flow may cause hypoperfusion and chronic ischemia, especially in border zones (Yamamoto and Bogousslavsky, 1998). There is a high prevalence of hypotension or labile blood pressure in vascular dementia and Alzheimer's disease (Passant et al., 1997) and hypoperfusion could contribute to the onset of dementia (Ruitenberg et al., 2005).

32.3.3. White matter lesions

White matter lesions are also termed white matter disease, white matter intensities, small vessel ischemic disease, or leukoaraiosis (Bogousslavsky, 1988). These lesions, seen on CT and MRI, are different from lacunes. White matter lesions are multifocal and become confluent with time. They are common in normal aging, but more frequent in vascular and degenerative dementia. Almost all cases of small-vessel dementia and two-thirds of Alzheimer's disease show white matter lesions (Brun and Englund, 1986; Ghika and Bogousslavsky, 1996). The nature of white matter lesions is not clearly elucidated and seems to represent a damaging process of vascular nature (small vessel disease). Severity of white matter lesions, especially in a periventricular location, has been associated with a diminished cognitive functioning (Mosley et al., 2005) and an increased risk of developing dementia (Prins et al., 2004).

32.3.4. Genetic factors

Genetic factors play a role in the etiology of vascular dementia. CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) for example, is a familial vascular encephalopathy, leading to strokes and vascular dementia (Chabriat et al., 1995; Joutel et al., 1996). Recently, it has been proposed that the e4 allele polymorphism of the apolipoprotein E genotype (APOE-e4) contributes to a higher risk of vascular dementia (Slooter et al., 2004). APOE-e4 on chromosome 19 was initially demonstrated to be involved in the pathogenesis of late-onset familial and sporadic Alzheimer's disease. It is a strong risk factor for the development of late-onset Alzheimer's disease (Saunders et al., 1993). The presence of APOE-e4 in an individual could increase by seven the risk of dementia after stroke (Breteler et al., 1997; Slooter et al., 1997).

32.4. Subtypes of vascular dementia

The clinical manifestations of vascular dementia depend upon the nature, location, and extent of the cerebral lesions. There are various terms and definitions for vascular dementia, which reflect the heterogeneous etiological mechanisms underlying the disease. Traditionally, vascular dementia is suspected when dementia occurs abruptly, is associated with focal neurological symptoms and follows a stepwise deteriorating evolution. However, vascular dementia may appear insidiously and present with a slow progressive course (Fischer et al., 1990).

32.4.1. Vascular dementia and vascular cognitive impairment

Vascular cognitive impairment is a term proposed by Hachinski (1994). The purpose of the vascular cognitive impairment concept is to take into account the complete range of severity of the cognitive deficits associated with cerebrovascular disease. The term vascular cognitive impairment is often preferred to vascular dementia, to emphasize the early recognition of cognitive impairment related to cerebrovascular disease, long before it becomes dementia. Vascular disease may lead to subtle cognitive changes, which in turn could be a warning sign of future dementia. This provides the clinician the

opportunity to identify individuals at risk and to institute preventive measures.

32.4.2. Post-stroke dementia

Post-stroke dementia (PSD) is characterized by an acute change in cognition and functional loss, after a cerebrovascular event. One-quarter of individuals will present dementia 3 months after a stroke (Tatemichi et al., 1990). Moreover, individuals with no cognitive impairment at the time of the acute event have an increased risk of developing cognitive impairment (Tatemichi et al., 1994). Post-stroke dementia may result from multiple large-vessel lesions, "strategic" vascular infarctions (Ferro, 2001), but may be degenerative in origin. As a matter of fact, data suggest that post-stroke dementia is not always of a vascular etiology. The observed incidence of Alzheimer's disease was 50% higher in stroke patients than in the general population (Kokmen et al., 1996).

32.4.3. Large-vessel dementia or multi-infarct dementia

One way to classify vascular dementia is based on the size of the vessel responsible (Brun, 1994). This approach is interesting, because the neuropathological etiology (Table 32.2) is considered. Large vessels comprising the carotid, circle of Willis, and their main branches are mainly concerned with arteriosclerosis, whereas the small vessels usually suffer from hypertensive angiopathy, resulting in different locations and size of strokes. Multi-infarct dementia or large-vessel dementia is a dementia due to large infarcts. Multi-infarct dementia is most often caused by thrombo-embolism of atherosclerotic lesions in large vessels, but can be cardiac in origin. Typical clinical features are lateralized sensory and motor deficits, combined with cognitive impairment and sometimes aphasia (Erkinjutti, 1987).

Table 32.2

The pathological classification of vascular dementia

Large-vessel vascular dementia
Multi-infarct dementia: multiple large infarcts cortical and/or subcortical
Small-vessel dementia
Subcortical ischemic vascular dementia
Lacunar state
Binswanger's disease
CADASIL
Cortical and subcortical infarct dementia
Strategic infarct dementia (SID): few infarcts in functionally important brain regions
Hypoxic/hypoperfusion dementia
Hypoxic encephalopathy
Borderzone infarcts
Hemorrhagic dementia
Subdural hemorrhage
Subarachnoid hemorrhage
Cerebral hemorrhage
Mixed dementia: Alzheimer's disease plus cerebrovascular disease

From Burn (2000).

32.4.4. Small-vessel dementia and Binswanger's disease

Small-vessel dementia relates to the pathology of arteriolar size vessels, mainly due to hypertension and hypoperfusion. Sometimes small-vessel dementia is due to microemboli of atheromatous large-vessel lesions or heart valves, amyloid angiopathy and arteritis. Small-vessel dementia may present as a cortical plus subcortical dementia or more often as a purely subcortical form, subcortical ischemic vascular dementia, which shows lacunar infarcts and arteriolar occlusion or widespread incomplete infarction of the white matter (Erkinjutti, 1987; Roman et al., 2002). Clinically small-vessel dementia is characterized by lacunar syndromes including motor hemiparesis, bulbar signs and dysarthria, emotional lability, and prominent executive dysfunction. Otto Binswanger described a dementia characterized by recurrent strokes and white matter changes at autopsy (Binswanger, 1894). This condition could represent the end-stage of a chronic hypertension process, but its entity remains controversial (Pantoni and Garcia, 1995).

32.4.5. Strategic (single stroke) infarct dementia

Single-strategic infarct dementia is a clinical picture characterized by the abrupt onset of cognitive deficits and behavioral changes in relation to a single infarct in specific regions of the brain. Strategic infarct dementia are described in small series and may follow ischemic lesion in the thalamus, the caudate nucleus, the lenticular nucleus, the angular gyrus, and the genu of the internal capsule (Benson et al., 1982; Bogousslavsky et al., 1988; Ott and Saver, 1993; Bathia and Marsden, 1994; Giroud et al., 1997; Annoni et al., 2003).

32.4.6. No stroke (infarct) or silent stroke dementia

The role of silent stroke in dementia is not well understood, but is well established. Silent brain infarcts are often found on neuroimages of old individuals (Longstreth et al., 1998) and could lead to a higher degree in cognitive decline in the affected elderly

(Vermeer et al., 2003). Pantoni et al. (1996) and Emery et al. (2005) reported three cases of progressive deterioration with prominent vascular lesions without clinical features of stroke.

32.4.6. Vascular dementia and Alzheimer's disease

Alzheimer's disease is estimated to be the most prevalent form of dementia (Cummings and Cole, 2002). Both Alzheimer's disease and stroke are more frequent with increasing age. Evidence has accumulated that cerebrovascular disease plays a major role in the development of dementia. First, Alzheimer's disease and vascular dementia may co-exist as a mixed form of dementia (Korczyn, 2002). Second, the presence of cerebrovascular disease and the occurrence of stroke may unmask or potentiate Alzheimer's disease. People with lacunar infarcts have a smaller degree of Alzheimer's disease pathology at autopsy, for clinical symptoms of dementia to be present (Snowdon et al., 1997; Schneider et al., 2004). Third, pathogenic mechanisms between Alzheimer's disease and cerebrovascular disease may act together synergistically. The pathology of Alzheimer's disease is characterized by beta-amyloid deposition in the brain, neurofibrillary tangles, and neuronal death. Cerebral ischemia may lead to amyloid accumulation and beta-amyloid affects vascular regulation. (Iadecola and Gorelick, 2003; Vagnucci and Li, 2003). Moreover, some vascular risk factors have emerged as risk factors for the development of Alzheimer's disease too (Skoog, 1998; Luchsinger et al., 2005). Whether Alzheimer's disease and vascular dementia are independent diseases or convergent pathologies remain uncertain (Casserly and Topol, 2004).

32.4.7. Cerebral amyloid angiopathy

Cerebral amyloid angiopathy is caused by the accumulation of beta-amyloid (Abeta) in vessels of the cortex and meninges. It is common in familial cerebral amyloidoses and in familial Alzheimer's disease. The most common clinical presentations of cerebral amyloid angiopathy are vessel rupture, lobar hemorrhage, and a progressive dementia.

32.4.8. The CADASIL syndrome

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a syndrome that includes strokes and cognitive impairment leading to vascular dementia. CADASIL is caused by mutations in the notch3 gene on chromosome 19 (Joutel et al., 1996). The transmission is autosomal dominant with 100% penetrance. Many families with CADASIL are described throughout the world (Chabriat et al., 1995; Chuah et al., 2001; Santa et al., 2003; Dotti et al., 2005). An autosomal recessive form (CARASIL) has been reported in Japan (Fukutake, 1999; Iwamoto et al., 2004). Clinical presentation includes recurrent subcortical ischemic strokes in early adult life; migraine with prolonged or unusual aura; cognitive deficits of subcortical patterns; and psychiatric disorders, especially mood disturbances. The phenotypes of CADASIL are widely variable; migraine can be the only clinical manifestation for example (Verin et al., 1995). The diagnosis of CADASIL is probably largely underestimated. MRI reveals bilateral, multifocal cerebral white matter lesions and subcortical infarcts. The anterior temporal pole, external capsule, basal ganglia, and sometimes the brainstem, are typically involved (Chabriat et al., 1998). Diagnosis is confirmed by genetic testing for notch3 mutations. Because of some false-negative results, individuals with a high clinical suspicion should be investigated by skin biopsy (Joutel et al., 2001).

32.4.9. Rare causes of vascular dementia

Some rare syndromes can lead to vascular dementia, especially in young patients, such as lupus and antiphospholipid syndrome (Asherson et al., 1987; Mosek et al., 2000); Sneddon syndrome (Wright and Kokmen, 1999); Buerger's disease (Rai et al., 2004); Fabry's disease (Mendez et al., 1997); giant cell arteritis (Caselli, 1990); angiotropic B cell endovascular lymphomas (Bille et al., 1995; Hayashi et al., 1995); relapsing polychondritis (Bichile et al., 1995); Spatz–Lindenberg's disease (Larner et al., 1999); CADASIL and other familial entities (St. Clair et al., 1995). Dural arteriovenous fistula or arteriovenous malformations can cause hypoperfusion and intellectual impairment (Datta et al., 1998). Coronary bypass (Raja et al., 2004), chronic obstructive pulmonary disease (Incalzi et al., 1993), and obstructive sleep apnea (Antonelli et al., 2004) can also be the etiology of vascular dementia.

32.5. Diagnosing vascular dementia

32.5.1. Diagnostic criteria

Several clinical criteria have been developed to standardize the diagnosis of vascular dementia. The criteria according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) (American Psychiatric Association, 1994) and to the International Classification of Diseases, 10th version (ICD-10) (World Health Organization, 1993) are very general (Tables 32.3 and 32.4). The NINDS-AIREN criteria

Table 32.3

The Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria

Multiple cognitive deficits manifested by both:
Memory impairment
At least one of these cognitive disturbances: apraxia, agnosia, aphasia or disturbance in executive functions
Significant impairment in social or occupational functioning as a result of the cognitive deficits, representing a significant decline from a previous level of functioning
Focal neurological signs and symptoms or laboratory evidence of cerebrovascular disease that are judged to be etiologically related to the disturbance
The deficits do not occur exclusively during the course of a delirium

From the American Psychiatric Association (1994).

Table 32.4

The criteria of the International Classification of Diseases, 10th version (ICD-10)

Dementia as defined by:
A decline in memory and other cognitive abilities that has been present for at least 6 months
Intact consciousness
A decline in emotional control or motivation, or a change in social behavior manifest as at least one of the following: emotional lability, irritability, apathy, coarsening of social behavior
Uneven distribution of deficits in higher cognitive functions
Focal brain damage, manifest as at least one of the following:
Unilateral spastic weakness of the limbs, unilaterally increased tendon reflexes, an extensor plantar response, pseudobulbar palsy
Evidence from the history, examination or tests of significant cerebrovascular disease, which may reasonably be judged to be etiologically related to the dementia

From the World Health Organization (1993).

(Roman et al., 1993) and the criteria of the State of California Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC) (Tables 32.5 and 32.6) (Chui et al., 1992) offer a more operative approach to the diagnosis of vascular dementia. The Hachinski Ischemic Score (HIS) (Hachinski et al., 1974) is a tool to differentiate Alzheimer's disease from multi-infarct dementia, once dementia has been established (Table 32.7).

Many limitations of these clinical guidelines have been underlined and their validity for clinical diagnosis is debated. First, because of an historical Alzheimer-based approach, these criteria emphasize memory impairment and an irreversible progression. The memory deficits that characterized Alzheimer's disease are not always observed in the initial stages of vascular dementia, which usually exhibits executive dysfunction (Hachinski, 1992). Moreover, the application of the different criteria produces a large variability in the rates of diagnosis (Gold et al., 1997, 2002; Hogervorst et al., 2003) (Table 32.8). Differences in the requirements of each set of criteria influence the specificity and the concordance of the criteria. The NINDS-AIREN criteria are the most specific of all available criteria and commonly applied in studies investigating therapies for vascular dementia. Neuroimaging play a crucial role in these criteria, which state that in the absence of relevant ischemic changes on CT/MRI the diagnosis of vascular dementia cannot be made.

32.5.2. Clinical assessment of vascular cognitive impairment and vascular dementia

The clinical diagnostic process should not derive from any single set of the diagnostic criteria described above. The assessment of a patient with suspected vascular cognitive impairment or vascular dementia should include a precise clinical history with the patient and his relatives, the evaluation of the patient's functional status and of his social support (Table 32.9). The clinical status should encompass a physical, neurological, and cognitive assessment associated with a psychiatric interview. The presence of risk factors, the evidence of cerebrovascular disease and its etiologic role in the clinical picture should be determined.

32.5.2.1. Cognitive symptoms

The definitions of vascular dementia and vascular cognitive impairment are mainly based on cognitive deficits. The identification of the extent and severity of cognitive impairment is important. The neuropsychological pattern has been defined in vascular dementia and compared to other dementia such as subcortical dementia and Alzheimer's disease. Relative to Alzheimer's disease, vascular dementia patients present more deficits in attention, concentration, and executive functions, and relatively less memory impairment (Kertesz and Clydesdale, 1994), but every cognitive function can be affected in vascular dementia.

32.5.2.2. Non-cognitive symptoms

Focal neurological deficits of vascular origin are numerous, well defined, and easy to recognize in clinical practice. These non-cognitive symptoms include focal deficits such as hemiparesis, corticospinal signs, visual field defects, parkinsonism, gait disorders, ataxia, focal dyskinesia, corticobulbar features, and

Table 32.5

The criteria of the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et L'Enseignement en Neurosciences (NINDS-AIREN)

Dementia definition	Decline in intellectual function affecting memory plus at least two other cognitive domains, sufficient to interfere with activities of daily living and not due to physical effects of stroke alone. Cases with disturbed consciousness and delirium are excluded.
Probable vascular dementia	Requires all the following: 1 Dementia 2 Cerebrovascular disease defined by: Focal signs on neurologic examination (such as hemiparesis, lower facial weakness, Babinski's sign, sensory deficit, hemianopia and dysarthria) Evidence of relevant cerebrovascular disease by CT or MRI —multiple large-vessel infarcts or —a single strategically placed infarct (angular gyrus, thalamus, basal forebrain, or PCA or ACA territories) or —multiple basal ganglia and white matter lacunes or extensive periventricular white matter lesions, or combinations thereof 3 A relationship between dementia and cerebrovascular disease, manifested by —dementia onset within 3 months of a stroke or —abrupt deterioration in cognitive functions or fluctuating stepwise course Clinical features consistent with the diagnosis of *probable vascular dementia* include the following: Early presence of a gait disturbance History of unsteadiness or frequent unprovoked falls Early urinary symptoms not explained by urologic disease Pseudobulbar palsy Personality and mood changes, abulia, depression, emotional incontinence, psychomotor retardation and abnormal executive function
Possible vascular dementia	May be made in the presence of dementia and focal neurological signs when: 1 No neuroimaging studies exist, or 2 In the absence of clear temporal relationship between stroke and dementia, or 3 There is subtle onset and variable course of cognitive deficit and evidence of cerebrovascular disease

From Roman et al. (1993).

urinary incontinence. These clinical hallmarks of cerebrovascular disease, very subtle in some cases, could be excellent diagnostic markers for vascular cognitive impairment and vascular dementia. Taking into account the entire clinical profile, including cognitive and non-cognitive symptoms, could represent a valid approach to diagnosing vascular cognitive impairment and vascular dementia (Ghika et al., 2006).

32.5.2.3. Behavioral and emotional symptoms

Numerous behavioral and emotional symptoms are associated with cerebrovascular disease, but none are pathognomonic of vascular dementia. Different types of affective disorders have been described, depression being the most prevalent, with a higher rate in vascular dementia than in Alzheimer's disease (Cummings et al., 1987; Robinson, 1997). Others include anxiety, increased sentimentality, inappropriate laughter, and pathological crying. Impaired emotional control is often associated with corticobulbar tract lesions. Changes in personality, psychotic reactions, hypomanic symptoms with elated mood and hyperactivity, apathy, and bipolar disorder are also encountered.

32.5.2.4. Laboratory investigations of vascular cognitive impairment and vascular dementia

Brain imaging in the evaluation of patients with dementia is recommended (Knopman et al., 2001). Both NINDS-AIREN and ADDTC criteria include neuroimaging to distinguish between vascular dementia and Alzheimer's disease. According to the NINDS-AIREN consensus, a diagnosis of probable vascular dementia is retained if focal neurologic signs and imaging evidence of cerebrovascular disease are associated with dementia. MRI is preferred to CT to demonstrate the various types of cerebrovascular disease in relevant regions and to eventually identify the underlying mechanisms (Van Straaten et al., 2004).

Table 32.6

The criteria of the State of California Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC)

Dementia definition	Deterioration in intellectual function sufficient to interfere with customary affairs of life, which is not isolated to a single category of intellectual performance and is independent of the level of consciousness.
Probable vascular dementia	Requires all the following: 1 Dementia 2 Evidence of two or more strokes by history, neurological signs, and/or neuroimaging; or a single stroke with a clear temporal relationship to the onset of dementia 3 Evidence of at least one infarct outside the cerebellum by CT or T1-weighted MRI The diagnosis of probable vascular dementia is supported by: 1 Evidence of multiple infarcts in brain regions known to affect cognition 2 History of multiple transient ischemic attacks 3 History of vascular risk factors (e.g., hypertension, heart disease, diabetes mellitus) 4 Elevated Hachinski Ischemic Score
Possible vascular dementia	1 Dementia and one or more of the following: 2a History or evidence of a single stroke without a clear temporal relationship with dementia onset, or 2b Binswanger's disease that includes all the following: —early onset of urinary incontinence or gait disturbance —vascular risk factors —extensive white matter changes on neuroimaging

From Chui et al. (1992).

Table 32.7

The Hachinski Ischemic Score (HIS)

Item	Score
Abrupt onset	2
Stepwise progression	1
Fluctuating course	2
Relative preservation of personality	1
Nocturnal confusion	1
Depression	1
Somatic complaints	1
Emotional incontinence	1
History of hypertension	1
History of strokes	2
Evidence of associated atherosclerosis	1
Focal neurologic symptoms	2
Focal neurologic signs	2

From Hachinski et al. (1974).
A score over 7 suggests a vascular etiology to dementia.
A score ≤ 4 does not support a vascular etiology.

Table 32.8

Sensitivity and specificity of four sets of clinical criteria for vascular dementia

Clinical criteria for vascular dementia	Detection of pathologically vascular or mixed dementia	
	Sensitivity	Specificity
DSM IV	0.36	0.89
ADDTC, possible vascular dementia	0.52	0.87
NINCDS-AIREN, possible vascular dementia	0.41	0.91
ICD-10	0.19	1.00
ADDTC, probable vascular dementia	0.21	0.96
NINCDS-AIREN, probable vascular dementia	0.19	0.98

From Gold et al. (2002).

This could represent multiple or strategic single infarcts, hemorrhages, multiple lacunes, extensive white-matter lesions, or a combination of these.

32.6. Treatment options in vascular dementia

Stroke being an important risk factor for vascular dementia, one might think that every treatment decreasing the risk of cerebrovascular disease should also protect cognitive functions. However, studies demonstrating clearly a benefit in treating every vascular factor to prevent or treat dementia are lacking. Therapeutic interventions for vascular dementia are largely limited to secondary prevention strategies.

Table 32.9

Clinical assessment of vascular dementia and vascular cognitive impairment

Clinical interview	*Information obtained from the patient and the caregiver*
	Onset, course, and nature of cognitive difficulties
	Onset, course, and nature of neurological symptoms
	Presence of behavior modifications and mood changes
	Presence of cerebrovascular risk factors
	Assessment of functional status
	Familial and social surrounding
Clinical examination	General physical examination
	Cognitive assessment
	Examination for focal neurologic signs
	Behavioral and thymic evaluation
Routine investigations	Evidence of cerebrovascular disease
	Evidence of risk factors
	Brain imaging
Specialized investigations	Neuropsychologic assessment
	Cranial and extra-cranial arteries, Doppler
	Echocardiography, Holther
	Functional brain imaging
	Cerebrospinal fluid examination

Control of blood pressure is important to decrease the rate of stroke (Chobanian et al., 2003) and probably of white-matter lesions (Goldstein et al., 2005), which is a risk factor for stroke and dementia. There are two clinical randomized trials on the treatment of hypertension that study dementia as an outcome. In the Syst-Eur prospective study (Forette et al., 2002), the treatment of systolic hypertension of old individuals induced a half decrease in the risk to develop dementia, Alzheimer's disease, and vascular dementia. The treatment of 1,000 patients during 5 years helped prevent 19 cases of dementia. The PROGRESS study, showed a diminished risk of dementia after a new stroke, among individuals with a past stroke treated for hypertension, even in normotensive patients (Lithell et al., 2003). Longitudinal studies demonstrated that the risk of vascular dementia was lower for individuals under hypertensive drugs (in't Veld et al., 2001).

There are currently no recommended treatments for the cognitive impairment of vascular dementia (Doody et al., 2001). Because of the evidence for cholinergic deficits in vascular dementia similar to Alzheimer's disease (Kalaria and Ballard, 1999; Mesulam et al., 2003), cholinesterase inhibitors have been studied in vascular dementia. In clinical trials, some benefits of galantamine in patients with Alzheimer's disease and cerebrovascular disease have been observed (Erkinjuntti et al., 2002). Donepezil and rivastigmine demonstrated improvements in cognition and global function compared to placebo too (Moretti et al., 2003; Wilkinson et al., 2003). The cognitive and functional benefits of cholinesterase inhibitors in vascular dementia or mixed dementia, is of a similar magnitude to those reported for Alzheimer's disease. It represents an equivalent in a 4–6 month delay in cognitive decline. Response to cholinesterase inhibitors is variable, with a significant proportion of treated individuals not responding. Memantine, an antagonist of the N-methyl-D-aspartate (NMDA) receptor, used for patients with moderate to severe Alzheimer's disease, showed minimal effects in vascular dementia (Orgogozo et al., 2000).

The medications currently available provide modest clinical improvements. Enhancing cholinergic function may be an effective treatment strategy for vascular dementia. New preventive ways are emerging, such as interventions from brain insulin receptors, statin therapy, dietary interventions, and lowering homocystein serum. The control of cardiovascular risk factors represents important strategies to prevent or slow the progression of dementia, by preventing recurrent stroke. Interventions in midlife may provide an important opportunity to preserve cognitive vitality later in life.

32.7. Conclusions

Vascular dementia, the commonest cause of dementia after Alzheimer's disease, is a complex entity, emerging from a variety of cerebrovascular pathologies. With the progressive ageing of the population, cerebrovascular disease will become more prevalent. Vascular dementia will increase, as an etiology of dementia, but also as a contributor to the degenerative dementia. Considering both Alzheimer's disease and vascular dementia pathology as causes for cognitive decline in older individuals will be increasingly appropriate in a clinical perspective.

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Chapter 33

"Silent" cerebral infarcts and microbleeds

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33.1. Introduction

Several decades ago neuropathologists reported the autopsy finding of multiple cerebral infarcts which were not associated with overt clinical symptoms (silent cerebral infarcts, or SCIs), and pointed to the existence of substantial subclinical vascular disease (Fisher, 1965, 1969; De Reuck et al., 1981; Fisher, 1991). However, for obvious methodological reasons little could be told from these findings on the clinical impact and prognostic significance of the SCIs detected.

The topic entered a second era with the introduction of modern neuroimaging techniques which permitted the identification of SCIs during life. Silent infarcts were incidentally recognized in patients who underwent computerized tomography (CT) in the investigation of acute stroke, and during the 1980s several such reports appeared. Subsequently, CT has largely been replaced by magnetic resonance imaging (MRI) which is much more sensitive for this purpose.

A third era started in the 1990s with neuroimaging studies of samples of healthy individuals in the general population, followed by correlative studies of silent infarcts and cognition, mood, and other neuropsychological features. Later on, longitudinal clinical and neuroimaging studies were performed to study the progression and prognostic impact of SCIs in these populations.

More recently the frequent presence of microbleeds (microhemorrhages) in the brain has been recognized. Similar to SCIs, silent cerebral microbleeds (CMBs) were first recognized in neuropathological studies, sometimes in conjunction with small brain infarcts (Fisher, 1971). However, recognition of CMBs on neuroimaging has come later than for SCIs because identification of CMBs requires specific MRI protocols.

More comprehensive knowledge on the high prevalence, clinical significance, and important prognostic implication of SCIs and CMBs has only recently become available, and has drastically changed the perspective of relative proportions between silent cerebrovascular disease and lesions which are readily apparent clinically. Silent vascular brain lesions far outnumber symptomatic cerebrovascular disease presenting as transient ischemic attacks (TIAs) and stroke: based on a provisional estimate, 11 million first silent MRI infarcts and hemorrhages would occur in the USA compared with only 770,000 patients with clinically apparent stroke—a 15-fold difference (Leary and Saver, 2003).

33.2. Definitions and terminology

Several publications have used the term *silent stroke* to denote brain infarcts and microhemorrhages in people without a history of TIA or stroke. However, the term *stroke* is not appropriate in this context, because this term is restricted to vascular lesions of the brain which cause clinical symptoms lasting more than 24 hours (Hatano, 1976). Purely descriptive terms like *silent cerebral infarct* and *microhemorrhage* (or *microbleed*) are therefore to be preferred.

As discussed below, there are several reasons why a vascular lesion in the brain may not give rise to clinical symptoms, may fail to be recognized, or may be misdiagnosed. The term *unrecognized*, rather than *silent*, has been proposed to allow for the possibility that symptoms may have occurred in some patients. The term *silent* is also challenged by more recent population-based studies which show that incidentally detected lesions in the brain are important determinants for cognitive impairment and dementia. Another

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proposed term is therefore *covert* infarcts, implying less dramatic presentations than acute cerebrovascular symptoms. However, this term is probably less well known among professionals, and possibly more difficult to communicate to lay persons.

Thus, neither term (silent, unrecognized, or covert) is ideal in all aspects. In the present review the terms *silent brain infarct* (SCI) and *cerebral microbleed* (CMB) are used, denoting vascular brain lesions detected either by autopsy or neuroimaging and without a corresponding history of acute cerebrovascular symptoms.

33.3. Silent brain infarcts

33.3.1. Clinical caveats in diagnosis of silent brain infarcts

Localization and size are obvious determinants if a brain lesion will cause clinical symptoms or be asymptomatic: silent infarcts can obviously go undetected if they occur in clinically ineloquent regions of the brain. However, there are also a number of clinical caveats in determining that a visualized brain infarct has indeed not been associated with any clinical symptoms.

First, previous clinical symptoms may be forgotten by the patient, or the clinical history may be incomplete. Self-reports tend to underestimate the number of people who have had stroke or TIA (Phillips et al., 1990), even in those who have sought medical attention and been adequately diagnosed and informed. In the Rotterdam Scan Study (Vermeer et al., 2003a), 8 of 42 participants with symptomatic infarcts during follow-up reported no previous history of stroke or TIA themselves, although this was documented in their medical records. Therefore, in scientific studies of silent infarcts, history should ideally be supplemented by check-up of previous medical records.

Second, symptoms may have occurred but were not recognized as possible stroke, or a health problem needing medical assessment, by the patient. It is well known that awareness of stroke symptoms is far from ideal in the population. Furthermore, there appears to be a systematic under-recognition of TIAs and stroke in the right hemisphere. Analysis of a large German database of more than 20,000 patients (Foerch et al., 2005) showed that 56% of all events were localized to the left hemisphere versus 44% to the right ($p < 0.001$), confirming the results of a previous study (Norrving and Bogousslavsky, 1991). There were no asymmetries for intracerebral hemorrhage, whereas all types of ischemic stroke were significantly more common in the left hemisphere. The asymmetry was especially pronounced in patients with transient and minor symptoms. The most likely explanation is that ischemia in the left hemisphere often causes dysphasia (sometimes as an isolated symptom), which is usually clinically well apparent, whereas non-dominant hemisphere ischemia can for example be associated with neglect.

Third, even if a patient seeks medical advice, some neurological symptoms may not be recognized as stroke by a physician. For example there are studies to show that cerebellar infarcts may sometimes present as an isolated vestibular dysfunction without clear focal signs (see Chapter 26), and thalamic and caudate infarcts may give rise to a broad spectrum of cognitive symptoms and mood changes, sometimes in isolation, which are a diagnostic challenge (see Chapter 25).

Fourth, it is well known that symptoms of TIA may result from an infarct visualized by neuroimaging (see Chapter 49). In the Rotterdam Scan Study (Vermeer et al., 2002a), 16 of 42 patients judged to have a symptomatic infarct reported symptoms corresponding only of TIA. Conceivably, a proportion of all TIAs may occur during sleep and pass unrecognized.

However, in total, these caveats are likely to account only for a small proportion of all silent infarcts. For example, under-recognition of right hemispheric stroke may account for about one-eighth of all ischemic strokes, a figure corresponding to only a few % of all silent infarcts in total (Leary and Saver, 2003). Apparently, the majority of infarcts judged as silent were probably not associated with acute focal neurological symptoms which were forgotten or misdiagnosed.

33.3.2. Neuroimaging caveats in diagnosis of silent strokes

Compared to autopsy detection of silent infarcts, neuroimaging is presumably more sensitive because at autopsy small lesions may be buried between brain slices and may not be visible at the cutting surface. However, there are also several diagnostic caveats in the imaging of silent cerebral infarcts, which could lead to over- as well as under-rating of silent lesions.

The early publications on neuroimaging of silent cerebral infarcts were all based on CT scans. The limitations of CT are well known and include limited resolution and the inability to separate previous bleedings from infarcts. Although CT has largely been replaced by conventional MRI, both techniques share some common problems. The separation of cortical atrophy from local tissue loss due to infarction is not always easy. In patients with symptoms of TIA or stroke and multiple lesions on CT or conventional MRI, it may be difficult to determine whether a visualized infarct is recent and symptomatic or old and clinically silent. This issue can now be solved by diffusion-weighted MRI if

performed in the acute phase. In this context it should also be recognized that a previously well-documented stroke may not always be visible as a "scar" on MRI. In the Cardiovascular Health Study (CHS) (Longstreth et al., 2002) follow-up MRI showed evidence for any infarct or bleed in only 59% of patients who were adjudicated as meeting the clinical criteria for stroke during follow-up.

On MRI, criteria for infarction include that the lesion should be visible both on T1-weighted (hypodensity) and T2-weighted (hyperdensity) images, in order to exclude punctuate unidentified bright objects seen only on T2-weighted images (Fig. 33.1). In the basal ganglia, presumed infarcts need to be carefully separated from enlarged perivascular (Virschow–Robin) spaces, a distinction which may have been overseen in early reports. In the lower third of the putamen, most hyperintense foci on T2-weighted images are known to represent perivascular spaces (Jungreis et al., 1988; Pullicino et al., 1995; Bokura et al., 1998), and this also holds true for a proportion of hyperintense foci in other parts of the basal ganglia (Takao et al., 1999). A size criterion (by only counting lesions >3 or >5 mm as infarcts) have sometimes been used to separate silent deep infarcts from perivascular spaces on proton-density scans, but perivascular spaces can occasionally attain larger sizes, up to 2–3 cm (Osborn et al., 2003). In comparing findings from different studies it should be recognized that evolution of MRI equipment with time has made the technique increasingly sensitive, and that imaging protocols may differ with respect to slice thickness and other details.

33.3.3. Silent cerebral infarcts in the general population and in selected patient groups without prior TIA or stroke

33.3.3.1. General population studies: prevalence

Several studies have shown that SCIs are often seen in healthy elderly in the general population. Cohort characteristics, prevalence data, risk factors, and associated conditions are summarized in Table 33.1. In the community-based Hisayama study (Shinkawa et al., 1995), the only population-based autopsy series on this topic, 12.9% of the 966 subjects examined had SCIs.

Some imaging studies have included persons who wished to receive health screening at their own expense (Kobayashi et al., 1991, 1997; Lee et al., 2000). Presumably, such a procedure incurs some selection of subjects; for example, with respect to socioeconomic status; and the mean age of subjects has been relatively low. In the largest study (Lee et al., 2000) of 994 subjects with a mean age of 49 years, the prevalence of SCIs increased with age, from 1.7% in those 40–49 years old to 43.8% among those 70–79 years old.

Importantly, comprehensive data based on MRI examinations of more unselected cohorts are now available from several population-based studies (Lindgren et al., 1994; Bryan et al., 1997; Price et al., 1997; Howard et al., 1998; Longstreth et al., 1998; Bryan

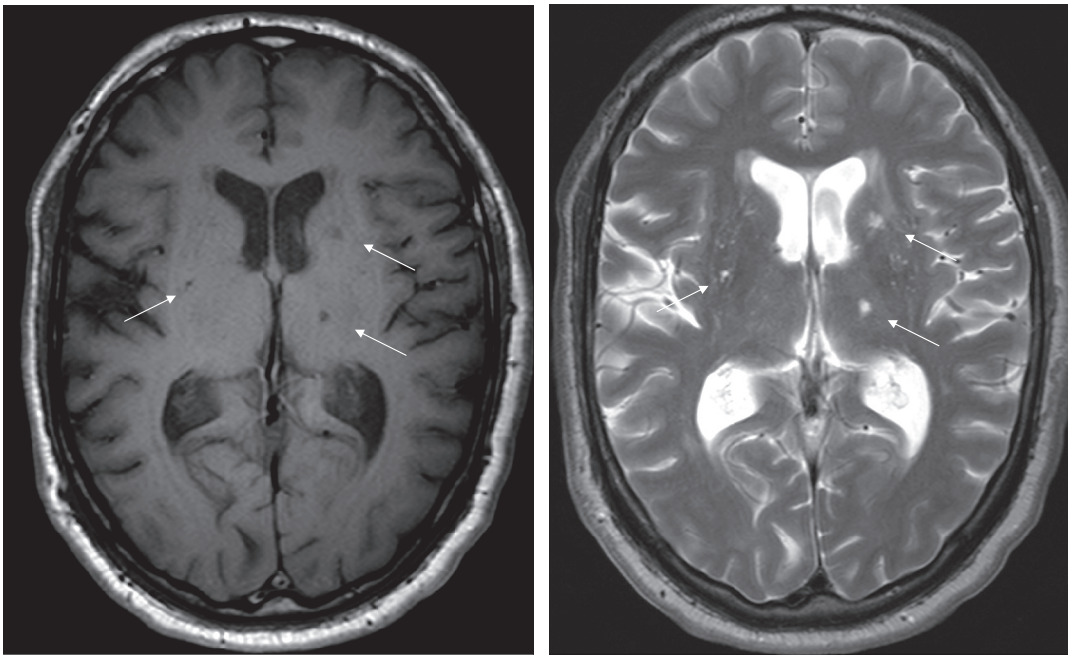

Fig. 33.1. Silent infarcts (arrows) in bilateral basal ganglia regions on MRI T1 (left) and T2 (right). Courtesy of Stig Holtås, Lund.

Table 33.1

Prevalence of silent cerebral infarcts in the general population

Reference	Cohort characteristics	*n*	Prevalence of SCI	Risk factors and associated conditions
Kobayashi et al., 1991	Persons wishing to undergo health screening (MRI)	246	13%	Low cerebral blood flow
Lindgren et al., 1994	Population based, age- and sex-matched to stroke patients (MRI)	77	9.1%	N.R.
Shinkawa et al., 1995	Population based autopsy study (Hisayama study)	966	12.9%	Age, systolic and diastolic blood pressure, atrial fibrillation
Kobayashi et al., 1997	Persons wishing to undergo health screening (MRI)	933	10.6%	Age, hypertension, diabetes, alcohol habits, retinal artery sclerosis
Price et al., 1997 Bryan et al., 1997	Population-based sample >65 years (Cardiovascular Health Study) (MRI)	3,660	28%	Symbol scores, neurological signs
Howard et al., 1998 Bryan et al., 1999	Population-based sample 55–72 years (ARIC study) (MRI)	1,737	11%	Age, hypertension, smoking, black race
Lee et al., 2000	Persons wishing to undergo health screening (MRI)	994	5.8%	Age, hypertension. Lower risk for mild alcohol consumption
Vermeer et al., 2002a	Population-based sample 60–90 years old (MRI)	1,077	24%	Hypertension, female gender
Liebetrau et al., 2004	Population-based sample of 85-year-old subjects (CT)	239	8.6%	N.R.
DeCarli et al., 2005	Population-based sample (MRI)	2,081	12.3%	Age

N.R.: not reported.

et al., 1999; Vermeer et al., 2002a; Liebetrau et al., 2004; DeCarli et al., 2005). Although participants in such studies tend to be somewhat healthier than average, probably leading to some underestimation of the prevalence of vascular disease, data from these studies nevertheless provide the most solid evidence available on characteristics of SCIs in the general population. Several of the studies have also separately published data on long-term prognosis, relationships with white matter disease, and clinical concomitants.

The Cardiovascular Health Study (CHS) (Bryan et al., 1997; Price et al., 1997) of 3,660 subjects over 65 years of age, found a prevalence of SCI of 31–36% among all participants, and 28% among those without known prior stroke. The Atherosclerosis Risk in Communities (ARIC) study of 1,737 persons found a lower prevalence, but ARIC involved a younger cohort (55–72 years) than the CHS (Howard et al., 1998; Bryan et al., 1999). Age specific prevalences in the two studies appear to compare well.

In the Rotterdam Scan Study (Vermeer et al., 2002a) 1,077 persons 60–90 years of age were examined with cerebral MRI. For 259 participants (24%) one or more infarcts on MRI were seen: 217 patients had only SCIs, and 42 had symptomatic infarcts. Thus, SCIs were five times as prevalent as symptomatic brain infarcts (Fig. 33.1). Prevalence of SCIs increased with age, from 8% in the 60–64-year-old patients to 35% among those 85–90 years old, and were more frequent in women (age-adjusted OR = 1.4; 95% CI = 1.0–1.8).

More recently, data on SCIs from the Framingham heart study (DeCarli et al., 2005) have been reported. In this large, population-based cohort of 2,081 subjects across a wide range of ages (from 34 to 97 years), the overall prevalence was 12.3%, nearly identical for both genders. As in previous reports, SCIs were common after age 50 and increased linearly with age.

With respect to morphological characteristics of SCIs, findings from the different studies are quite consistent (Kobayashi et al., 1991; Lindgren et al., 1994; Shinkawa et al., 1994; Bryan et al., 1997; Kobayashi et al., 1997; Price et al., 1997; Howard et al., 1998; Longstreth et al., 1998; Bryan et al., 1999; Lee et al.,

2000; Vermeer et al., 2002a). SCIs are usually small, with 60–93% being less than 1.5 cm in diameter, and about three-quarters are single. The majority (70–94%) are localized to basal ganglia or subcortical matter, whereas less than 15% are cortical. SCIs are localized to the pons or cerebellum in up to 15% of cases. Thus, the majority of SCIs share imaging characteristics of lacunar infarcts caused by subcortical penetrating artery disease (see Chapter 27).

33.3.3.2. Risk factors for silent cerebral infarcts

All studies accord in the steep, often linear, increase in prevalence of SCIs with age. A strong association with hypertension, with odds ratios between 2 and 3, is also a general finding across all studies. Besides systolic, diastolic, and pulse pressure, several studies have noted an association between SCIs and various other indices of blood pressure dysregulation, including nocturnal non-dipping (Kairo et al., 1996, 1997), ambulatory blood pressure and blood pressure variability (Shimada et al., 1990; Goldstein et al., 1998), and exaggerated blood pressure response to mental stressors (Waldstein et al., 2004). In hypertensive persons an association with silent brain infarcts and retinal microvascular signs was recently reported from the ARIC study (Cooper et al., 2006). Significant associations have also been seen between intimal media thickness in the carotid artery and silent infarcts (Longstreth et al., 1998; Shinoda-Tagawa et al., 2002; Vermeer et al., 2003a) as well as carotid stenosis (Hougaku et al., 1994).

Findings for other risk factors are more variable between studies. Diabetes was a risk factor in a study by Kobayashi et al. (1997), but not in other studies (Howard et al., 1998; Longstreth et al., 1998; Vermeer et al., 2002a). Metabolic syndrome was a risk factor in the study by Kwon et al. (2006); smoking was a risk factor in the ARIC study (Howard et al., 1998) but not in the Rotterdam study (Vermeer et al., 2002a); coexisting hypertension and diabetes increased the risk in the study by Eguchi et al. (2003); and atrial fibrillation was a risk factor in the Hisayama study (Shinkawa et al., 1994). The role of homocysteine as a risk factor is supported by a Japanese study (Matsui et al., 2001) and the Rotterdam Scan Study (Vermeer et al., 2002b), whereas data on the associated methylenetetrahydrofolate reductase (MTHFR) gene polymorphism are conflicting (Notsu et al., 1999; Kohara et al., 2003). Links with inflammatory indices (CRP and interleukin-6 levels) involved in atherosclerosis have also been reported (Hoshi et al., 2005; van Dijk et al., 2005).

Gender effects also differ between studies. Whereas a 30–40% increased risk was observed in the Rotterdam study (Vermeer et al., 2002a) and in the lacunar infarct substudy of the CHS (Longstreth et al., 1998), no difference was observed in other studies (Kobayashi et al., 1997; Howard et al., 1998; DeCarli et al., 2005).

33.3.3.3. Co-existence of silent brain infarcts and white matter ischemic lesions

Silent brain infarcts should not be regarded in isolation because they are closely linked to ischemic white matter lesions. White matter lesions are even more prevalent in the elderly than SCIs (Liao et al., 1996; Longstreth et al., 1996; de Leeuw et al., 2001), and the two conditions share most risk factors and show a high degree of co-variance (Kuller et al., 2004; DeCarli et al., 2005). White matter lesions are attributed to vascular alterations in long penetrating arteries and arterioles supplying the white matter. The vascular changes are characterized by hyaline wall thickening, smooth muscle cell loss, and narrowing of the vessel lumen. They ultimately impair autoregulatory adaptation to changes in cerebral blood flow and result in diffuse areas of reduced myelination (leucoaraiosis or white matter hyperintensities) (Pantoni and Garcia, 1997). White matter ischemic lesions are also commonly seen in Alzheimer's disease, suggesting possible alternative mechanisms to their development.

The concepts of white matter lesions and silent brain infarcts have evolved in parallel, and the large population-based studies (the CHS, ARIC, and Rotterdam studies) have comprehensively reported on both conditions (alone and in combination) with respect to prevalence, risk factors, associated conditions, and prognosis.

33.3.3.4. Silent cerebral infarcts in patients with other types of vascular disease

Patients with manifest vascular disease appear to be at risk for SCIs at a younger age (Table 33.2). In the SMART study (Giele et al., 2004), for patients with a mean age of 58 years with coronary heart disease, peripheral arterial disease, or abdominal aortic aneurysm, the prevalence of SCIs on MRI was 17%, comparable to the prevalence seen in population-based studies of healthy elderly in the age group 65–69 years. A wide range of risk factors for SCIs was identified in this study. SCIs are also common in patients with coronary heart disease (Modrego Pardo et al., 1998).

In early smaller series of patients with atrial fibrillation free from stroke, an SCI prevalence of up to 48% was reported (Petersen et al., 1987, 1989), whereas a prevalence of 14% was found in the SPINAF study (Ezekowitz et al., 1995) and 26% in the SPAF study (Feinberg et al., 1990). All of these studies were CT based.

Table 33.2

Prevalence of silent cerebral infarcts in patients with different types of vascular disease but no previous TIA or stroke

Reference	Cohort characteristics	*n*	Prevalence of SCI	Risk factors and associated conditions
Petersen et al., 1987	Chronic atrial fibrillation (CT)	29	48%	N.R.
Petersen et al., 1989	Paroxysmal atrial fibrillation (CT)	30	13%	N.R.
Feinberg et al., 1990	SPAF Study (atrial fibrillation) (CT)	141	26%	Age, left atrial size
Norris and Zhu, 1992	Carotid stenosis without TIA (CT)	115	30%	N.R.
Brott et al., 1994	ACAS Study without prior TIA/ stroke (CT)	848	15%	N.R.
Ezekowitz et al., 1995	SPINAF Study (atrial fibrillation) (CT)	516	15%	Age, hypertension, active angina, systolic blood pressure
Modrego Pardo et al., 1998	Coronary heart disease patients (CT)	100	30%	carotid atherosclerosis
Giele et al., 2004	Manifest vascular disease (MRI) blood pressure, creatinine, renal function, abdominal aortic aneurysm, homocysteine, intimal media thickness	308	17%	age, hypertension, systolic and diastolic

N.R.: not reported.

SCIs have also been studied in persons with asymptomatic carotid stenosis. A SCI prevalence of 30% (based on CT) was reported by Norris and Zhu (1992), whereas in the Asymptomatic Carotid Atherosclerosis Study (ACAS) (Brott et al., 1994) 15% of those with no history of stroke or transient attack (aged 40–79 years) had a silent cerebral infarct on baseline CT scan. Most infarcts were single, deep, and were evenly distributed ipsilaterally and contralaterally to the studied artery, but were significantly more frequent in the right hemisphere. Factors associated with silent infarction were abnormal gait, abnormal reflexes, but not degree of carotid stenosis.

33.3.3.5. Effects and prognostic implication of silent cerebral infarcts

The increasing recognition that SCIs are associated with cognitive decline, depressed mood, and increased risk for stroke represents a scientific advance of major importance for public health. Several cross-sectional studies have shown that SCIs are related to decreased cognitive functioning (Price et al., 1997; Longstreth et al., 1998; Matsui et al., 2001; Maeshima et al., 2002). Most studies have been done in middle-aged and elderly persons, but even in children with sickle cell disease studies show a relationship between SCIs and decreased cognitive function (Wang et al., 2001; Schatz et al., 2002). Similar associations with cognitive decline with SCIs have been reported for periventricular and subcortical white matter lesions (Longstreth et al., 1996; de Groot et al., 2000; Mosley et al., 2005). Co-existing high degree white matter ischemic lesions (WMHs) and silent infarcts appear to have independent, additive effects (Mosley et al., 2005). The cognitive effects of SCIs and white matter lesions presumably result from disruption and degradation of white matter pathways connecting functionally related cortical (particularly frontal) and subcortical structures.

Depression in the elderly appears also to be part of the spectrum of cognitive effects linked to SCIs: high prevalences (51–94%) of SCIs have been reported in patients with pre-senile or senile major depression (Fujikawa et al., 1993) and such findings have been associated with poor short-term response to antidepressant treatment (Fujikawa et al., 1996). In the CHS (Steffens et al., 1999) depressive symptoms were not only correlated with silent cerebral infarcts at baseline, but also persistence of depressive symptoms during follow-up (Steffens et al., 2002). Silent infarcts have also been associated with late-onset mania (Fujikawa et al., 1995). SCIs are also linked to subtle neurological abnormalities and gait disturbances in the elderly, currently under study in the LADIS project (van der Flier et al., 2005).

Longitudinal studies show that SCIs commonly progress, and that new SCIs are much more common than clinically apparent stroke (Vermeer et al., 2003a). In the CHS (Longstreth et al., 2002) 17.7% of the 1,433

participants developed incident SCIs over 5 years on follow-up MRI; over the same period only 2.7% of the participants experienced a clinically apparent stroke. Severity of white matter lesions on initial MRI was the strongest predictor of new SCIs, again demonstrating the close link between the two conditions.

The presence of SCIs, periventricular white matter lesions, and generalized brain atrophy at base-line. as well as their progression, are associated with a steeper cognitive decline on follow-up, in particular affecting information processing speed and executive function (de Groot et al., 2002; Longstreth et al., 2002; Kuller et al., 2005; Longstreth et al., 2005; Prins et al., 2005; Schmidt et al., 2005). In the Rotterdam Scan Study the risk of dementia more than doubled in persons with SCIs at baseline; this decline was restricted to people who had new SCIs during follow-up (Vermeer et al., 2003c).

Long-term follow-up studies have also showed that SCIs portend an increased risk for future clinical stroke, independent of other risk factors. Among patients with SCIs, the CHS study reported a 7.3% incidence of stroke within 4 years, representing a two-fold increased risk compared to persons without SCIs (Bernick et al., 2001). An even higher risk was found in the Rotterdam study (11.7% during 4.2 years among persons with SCIs at baseline), representing a four-fold increase in risk after adjustment for other risk factors. Also, for this outcome SCIs and white matter lesions appear to additively increase the risk (Vermeer et al., 2003b; Kuller et al., 2004).

33.3.3.6. Therapy of silent cerebral infarcts in persons without prior TIA or stroke

The vast majority of SCIs are small and deep and reflect penetrating artery disease, a pathogenesis shared with lacunar infarcts (see Chapter 27). As reviewed above, SCIs are associated with cognitive effects and increased rates of stroke which appear to be intermediate between those seen in the general population and among patients with a clinically apparent lacunar infarct (see Chapter 27). Should then the same principles applied in secondary stroke prevention also be applied in persons found to have SCIs? As yet, there is very little solid evidence to guide clinical practice on this issue. A comprehensive risk factor screen and adaptation of principles for vascular disease prevention in general appears well justified, given the associations with risk factors and SCIs. Among the modifiable risk factors, careful blood pressure control likely plays a major role in the long term.

With respect to antiplatelet therapy, risk estimates from observational studies without direct trial support in the specific population are currently not regarded as an adequate decision basis (though the topic has been debated). Thus, unless there is another clear indication present, SCIs per se are not currently regarded as an indication for an antiplatelet agent. In a Japanese study the antiplatelet agent cilostazol (geographically not widely licensed) prevented the onset of silent cerebral infarcts in subjects with type II diabetes (Shinoda-Tagawa et al., 2002), but this finding has not been replicated in further studies. In atrial fibrillation patients in the SPINAF study, anticoagulant therapy did not affect the rate of silent infarcts (Ezekowitz et al., 1995). No effect on statin therapy (pravastatin) on silent infarcts or progression of white matter lesions was observed in a substudy of the PROSPER trial (Ten Dam et al., 2005). There are no data on the role of homocysteine lowering therapy in this context. The low prevalence of carotid artery disease and cardioembolic sources associated with SCIs appears not to warrant the broad use of screening with ultrasound or echocardiography in the absence of physical signs at examination. Further research will have to show if preventive measures of people with SCI free from stroke and TIA should be more aggressive than the general principles for primary vascular prevention currently most widely used.

33.3.4. Silent cerebral infarcts in patients with symptomatic cerebral ischemia

33.3.4.1. Prevalence and risk factors

Several studies, summarized in Table 33.3, have documented that SCIs are frequently seen in patients admitted with a first TIA or stroke. Most of these studies are CT-based, which may reflect that many studies were performed before MRI became more widely available, but also that MRI is more difficult to perform in unselected patients with acute stroke than in healthy persons.

In the earlier studies (Chodosh et al., 1988; Kempster et al., 1988; Kase et al., 1989; Herderschee et al., 1992; Brainin et al., 1995) a relatively low prevalence (11–13%) of SCIs was reported, presumably related to the use of early-generation CT equipment. In later studies (Ricci et al., 1993; Boon et al., 1994; Jörgensen et al., 1994; Davis et al., 1996; Corea et al., 2001) higher prevalences ranging from 23% to 38% were found. Comparison of SCI rates between patients with TIA/stroke and healthy individuals is hampered by the lack of any large MRI-based study in stroke patients.

The presence of SCIs in stroke patients have been associated with a wide range of risk factors such as increasing age (Herderschee et al., 1992; Mounier-Vehier et al., 1993; Boon et al., 1994; Jörgensen et al., 1994; Davis et al., 1996), male sex (Ricci et al., 1993;

Table 33.3

Prevalence of silent cerebral infarcts in patients with TIA or stroke

Reference	Cohort characteristics	*n*	Prevalence of SCI	Risk factors and associated conditions
Chodosh et al., 1988	NINCDS Stroke Data Bank (CT)	1203	11%	Similar to stroke in general
Kempster et al., 1988	Atrial fibrillation and stroke (CT)	54	13%	N.R.
Kase et al., 1989	Framingham study (CT)	124	11%	Glucose intolerance
Herderschee et al., 1992	Dutch TIA study (CT)	2369	13%	Age, hypertension, smoking
Norris and Zhu, 1992	TIA and carotid stenosis (CT)	203	47%	N.R.
Streifler et al., 1992	NASCET study (CT)	352	34%	N.R.
Ricci et al., 1993	SEPIVAC study (CT)	209	38%	Male sex, hypertension, ischemic ECG changes
Mounier-Vehier et al., 1993	Hospital-based series of stroke and TIA	595	19%	Age and left atrial size
Brott et al., 1994	ACAS subjects with TIA (CT)	139	25%	N.R.
Jörgensen et al., 1994	Copenhagen stroke study (CT)	500	29%	Age, hypertension, male sex, claudication
Boon et al., 1994	Hospital-based series (CT)	755	27%	Age, hypertension
Brainin et al., 1995	Stroke data bank (CT)	618	11%	Hypertension
Davis et al., 1996	TOAST study (CT)	629	23%	Age, male sex, hypertension, black race
EAFT Study Group, 1996	EAFT study, atrial fibrillation patients (CT)	985	14%	N.R.
Corea et al., 2001	Lille stroke and dementia study (CT)	202	26%	Leucoaraiosis
Adachi et al., 2002	Hospital-based series (MRI)	171	61%	N.R.
Minn et al., 2005	Hospital-based series of stroke patients > 80 years old	38	76%	N.R.

Jörgensen et al., 1994; Davis et al., 1996), arterial hypertension (Hederschee et al., 1992; Ricci et al., 1993; Boon et al., 1994; Jörgensen et al., 1994; Brainin et al., 1995; Davis et al., 1996), cigarette smoking (Hederschee et al., 1992), atrial size (Mounier-Vehier et al., 1993), claudication (Jörgensen et al., 1994), glucose intolerance (Kase et al., 1989), leucoaraiosis (Corea et al., 2001), and black race (Davis et al., 1996).

As is the case for SCIs detected in healthy persons, SCIs in patients with TIA or stroke are most often (up to 85%) small and deep. Cortical infarcts account for 10–24% (Herderschee et al., 1992; Boon et al., 1994; Jörgensen et al., 1994), may more often involve the right hemisphere or the posterior cerebral artery territory than other cortical areas, and may more often be linked to a cardio-embolic cause (Chodosh et al., 1988; EAFT Study Group, 1996). With respect to subtype of presenting stroke, three studies (Boon et al., 1994; Corea et al., 2001; Adachi et al., 2002) reported that SCIs were more prevalent in patients with lacunar infarction than in those with atherothrombotic or cardio-embolic infarcts. With respect to less common causes of stroke, SCIs are characteristically part of the spectrum of neuroimaging findings in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) (see Chapter 47).

33.3.5. Clinical effects of silent cerebral infarcts in patients with TIA or stroke

Several studies have reported that mortality and morbidity is not influenced by the presence of SCIs in cohorts of patients with stroke or TIA (Chodosh et al., 1988; Ricci et al., 1993; Boon et al., 1994; Jörgensen et al., 1994; Brainin et al., 1995; Corea et al., 2001). However, relatively crude outcome measures and short times of follow-up (ranging from 1 month up to 3 years) have been used in these studies.

In contrast, prognostic implications of SCIs have been found in some other studies. In the Dutch TIA study, residual symptoms of any kind were more common in patients with SCIs than in those without (Herderschee et al., 1992), and both SCI and white matter lesions were associated with an increased risk of recurrent stroke (Van Swieten et al., 1992; Dutch TIA

Study Group, 1993). Corea et al. (2001) also found that SCIs incurred a higher risk of recurrent stroke. The EAFT study of patients with stroke and atrial fibrillation also reported an association between SCIs at baseline and an increased risk of vascular events in general and of recurrent stroke in particular (EAFT Study Group, 1996).

The relationship between SCIs and prognosis is complex because SCIs are linked to stroke subtype which by itself affects prognosis: SCIs are more prevalent in lacunar infarcts, which are relatively small and carry a more favorable short-term prognosis than other stroke subtypes (Norrving, 2003). Prognostic studies limited to patients with lacunar infarcts show that SCIs as well as white matter lesions affect prognosis in this stroke subtype. In four studies (Kazui et al., 2001; Staaf et al., 2001; De Jong et al., 2002; Yamamoto et al., 2002) SCI, hypertension, diabetes, and presence of any cardio-embolic source were independent predictors of future stroke risk, and presence of SCIs may also affect long-term survival (De Jong et al., 2002). Presence of SCIs and white matter lesions have also been found to be independent predictors of worse functional outcome (Samuelsson et al., 1996; De Jong et al., 2002), suggesting that more advanced small-artery disease may limit the possibility of functional recovery of the brain after a small focal lesion.

There is also mounting evidence that SCIs are an important risk factor for mild cognitive impairment and dementia after stroke. A recent study found that early post-stroke territorial infarction, older age, and lower education were predictive factors for vascular mild cognitive impairment whereas SCIs and white matter lesions became more important in a longer perspective (Rasquin et al., 2004). Several studies have identified SCIs as an independent predictor for post-stroke dementia (for a review see Leys et al., 2005). The influence of SCIs seems to become more important when the delay between stroke and the cognitive assessment is longer, illustrating the need for long-term follow-up studies to determine the influence of SCIs after stroke.

33.3.6. New silent infarcts after stroke

As is the case for SCIs in the general population, SCIs progress with time in patients with TIA and stroke. The issue has so far mainly been investigated in patients with lacunar infarcts. In this stroke subgroup, new silent infarcts develop at a rate of at least twice that of new symptomatic lacunae (for a review see Norrving, 2003), and after about 3 years, almost half of all patients had developed silent infarcts as well as progression of leucoaraiosis (Van Zagten et al., 1996). However, there are as yet no data on the clinical effects of progressing SCIs with time in these patient groups.

More recently, a new dimension in the study of SCIs has been introduced with the use of diffusion-weighted MRI in the early phase after acute stroke. In a general stroke population of hospital-based patients, the rate of new lesions seen on MRI at 1 week was 34% (Kang et al., 2003b). Most of these events were clinically silent with only 2% having evidence of clinical recurrence. Another recent study found a 10% rate of new lesions on diffusion-weighted MRI 1 month after TIA or minor stroke and half of these new lesions were asymptomatic (Coutts et al., 2005). Complexity is also increased by the diffusion-weighted MRI finding that almost half of all acute ischemic strokes show up as multiple ischemic areas in single or multiple vascular territories, a pattern almost as common as the traditional acute ischemic stroke concept of a single, focal lesion (Kang et al., 2003a). Clearly, later imaging studies are faced with uncertainties in determining which of the multiple lesions should be considered symptomatic and which should be regarded as silent.

33.3.7. Therapy

There is a paucity of clinical trial and observational data on therapeutic issues with respect to SCI in patients with TIA and stroke. Although there is some evidence that SCIs at baseline affect prognosis, it is unknown if more aggressive secondary preventive approaches than those generally applied are warranted. Benefits of combining antithrombotic regimens may well be offset by increased adverse effects, as illustrated by the recent MATCH trial (Diener et al., 2004).

Blood pressure control likely plays a major role in secondary stroke prevention. A CT substudy of the PROGRESS trial on blood-pressure-lowering therapy in patients with stroke found no significant effect of therapy on the rate of silent brain infarcts over 3.9 years (Hasegawa et al., 2004), whereas an MRI substudy showed that the blood-pressure-lowering regimen stopped or delayed the progression of white matter lesions (Dufouil et al., 2005). Theoretical concerns have been raised that too-aggressive blood pressure lowering may have adverse effects in patients with advanced small-vessel disease and impaired autoregulation (Birns et al., 2005). With respect to carotid surgery there are no data to support that the presence of SCIs should affect the decisions whether to operate or not. Because new SCIs are at least as common as clinically apparent ones, SCI may be useful surrogate

outcomes in future clinical trials, a strategy that has proved to be very successful in multiple sclerosis.

33.4. Cerebral microbleeds

Cerebral microbleeds (CMBs) (Offenbacher et al., 1996) are small (2–5 mm) hypointense lesions on gradient-echo MRI, which result from rupture of small blood vessels most commonly in the basal ganglia or subcortical white matter. The common occurrence of CMBs has only been recognized for about a decade. Current knowledge, recently comprehensively reviewed (Koennecke, 2006; Viswanathan and Chabriat, 2006; Cordonnier et al., 2007), is still far from complete but in rapid development.

33.4.1. Neuroimaging characteristics

Gradient-echo (GE) or T2*-weighted MRI is a highly sensitive technique in the detection of old and recent cerebral hemorrhage (Fig. 33.2). Hemosiderin remains permanently stored at sites of previous bleedings and the appropriate MRI sequences thus visualizes the cumulative burden of previous CMBs. Autopsy studies have confirmed that the small hypointense foci on GE MRI correspond to perivascular hemosiderin-laden macrophages and ischemic necrosis, and are residues of small hemorrhages due to rupture of vessels smaller than 200 µm (Fazekas et al., 1999; Tanaka et al., 1999). Neuroimaging criteria are available to separate CMBs from flow voids of vessels, calcium, or iron deposits in the basal ganglia, and cerebral cavernous malformations (Koennecke, 2006; Viswanathan and Chabriat, 2006).

33.4.2. Prevalence of cerebral microbleeds in different populations

In cohorts of persons without cerebrovascular disease the prevalence of CMBs average 5.7% (range 4.5–7.7%) (Koennecke, 2006). CMBs increase with age; however, the association with hypertension is not consistent, perhaps for methodological reasons. In the Austrian Stroke Prevention Study (Robb et al., 1999) there was a co-linear relationship between CMBs, SCIs and white matter lesions, for which the importance of chronic hypertension is well established. Prevalence appears not to differ substantially according to ethnicity.

In cohorts of patients with ischemic stroke the average prevalence of CNBs is 40%, with highest rates (up to 57%) in patients with ischemic cerebral small-vessel disease (SCI and white matter lesions) (Koennecke, 2006). Chronic hypertension has appeared as a risk factor in several, but not all studies. CMBs appear to be more prevalent among subjects of Asian origin compared with Caucasians, but this finding may be linked with differences in patient selection criteria. In contrast to ischemic stroke, the prevalence of CMBs

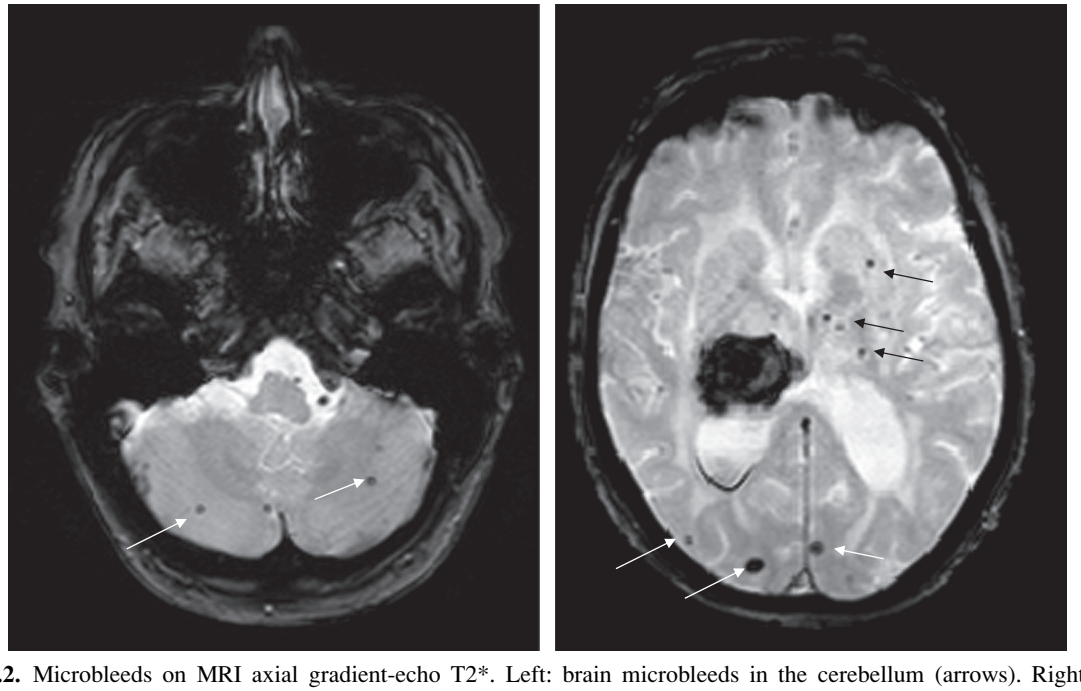

Fig. 33.2. Microbleeds on MRI axial gradient-echo T2*. Left: brain microbleeds in the cerebellum (arrows). Right: brain microbleeds in deep and subcortical locations (arrows) and an intracerebral hemorrhage in the left thalamus and internal capsule. Courtesy of Charlotte Cordonnier, Lille.

has been found to be very low (2%) among patients with TIA (Werring et al., 2005).

The prevalence of CMBs is particularly high among patients with intracerebral hemorrhage, ranging from 47% to 80% (mean 68%) (Koennecke, 2006); thus, CMBs are about 10 times more common in this population than in the healthy elderly. Interestingly, an independent association of CMB with lower cholesterol levels was reported in one study (Lee et al., 2002).

CMB is also associated with cerebral amyloid angiopathy which is the primary cause of primary lobar intracerebral hemorrhage in the elderly. The presence of multiple, strictly lobar hemorrhages, including CMBs, has been shown to be highly specific for severe cerebral amyloid angiopathy in elderly patients with no other definitive cause of intracerebral hemorrhage (Knudsen et al., 2001; Viswanathan and Chabriat, 2006), and is an important prerequisite to establish the diagnosis of cerebral amyloid angiopathy in life (Greenberg et al., 1996; Knudsen et al., 2001; Rosand et al., 2005). CMBs are also a characteristic imaging feature of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) (see Chapter 47). CMBs are also seen in about a quarter of patients with Alzheimer's disease (Koennecke, 2006), presumably related to coincidence with cerebral amyloid angiopathy.

33.4.3. Clinical significance and prognostic implications

Cerebral amyloid angiopathies had been thought to be clinically silent, but the issue is methodologically complex because they often coexist with SCIs and white matter lesions which are known to cause cognitive impairment. However, a recent study which matched for the presence of SCIs and white matter lesions found that CMBs were associated with cognitive impairment, mainly executive dysfunction (Werring et al., 2004). Hypothetically, CMBs may affect cognition through tissue loss in the frontal lobes and basal ganglia disrupting frontal–basal ganglia connections.

The prognostic implications of CMBs are currently uncertain. Small studies have shown that CMBs may increase the risk of intracerebral hemorrhage and possibly also ischemic stroke (Fan et al., 2003). Further longitudinal studies are needed to clarify these issues further. In cerebral amyloid angiopathy, a longitudinal study showed that 50% of patients had experienced new, frequently multiple CMBs at MRI 16 months later (Greenberg et al., 2004). The number of baseline CMBs increased the risk of cognitive impairment, functional dependence, or death. It is also currently uncertain if CMBs potentiate the risk for intracerebral hemorrhage in patients treated with antiplatelet agents, anticoagulants, and intravenous thrombolytic therapy (Koennecke, 2006; Viswanathan and Chabriat, 2006).

33.5. Conclusions and directions for future research

A synopsis of our current knowledge of silent infarcts and microbleeds is given in Table 33.4. During the last 1–2 decades, silent brain infarcts and microbleeds have evolved from innocent bystanders in patients with TIA or stroke, to small lesions of major importance for vascular and mental health in the population. Silent cerebrovascular disease is clearly not innocuous: in the general population it is linked to cognitive impairment, dementia, and increased risk for stroke;

Table 33.4

Silent cerebral infarcts and microbleeds: a synopsis of current knowledge

1. Silent brain infarcts are highly prevalent in the elderly population: patients with manifest vascular disease are at risk for silent infarcts at a younger age.
2. Age and hypertension are the most consistent determinants for silent infarcts, whereas the associations with other vascular risk factors are inconsistent.
3. SCI is associated with cognitive impairment, mood changes, and gait disturbances, and carries an increased risk of future stroke, cognitive decline and dementia.
4. SCI and white matter lesions commonly coexist and appear to have additive effects.
5. SCI are also highly prevalent among persons with TIA and stroke. In these patients, SCI appears not to influence the short-term prognosis but quite crude outcome measures have been used so far. In patients with lacunar infarcts, SCIs and white matter lesions at index stroke has been shown to adversely affect prognosis.
6. SCI is a risk factor for post-stroke dementia.
7. Therapy to prevent SCI, or further negative consequences once SCI are present, remains to be established. Risk factor screening and intervention are probably crucially important.
8. Cerebral microbleeds CMBs result from underlying small-vessel pathologies such as hypertensive vasculopathy or cerebral amyloid angiopathy.
9. Prevalence of CMBs is circa 5% in the elderly population, circa 40% in patients with ischemic stroke, and circa 70% in patients with hemorrhagic stroke.
10. More prospective data are needed to assess the prognostic implications of CMBs.

and in stroke patients there is a growing amount of evidence that the presence and extent of silent infarcts at the time of the first stroke have significant prognostic implications for almost all outcomes. As yet, very little is known with regard to primary and secondary preventive measures in silent cerebrovascular disease. Hopefully the observational phase delineating the detrimental consequences of silent cerebrovascular disease will soon be followed by focused therapeutic trials in this field.

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Chapter 34

Spinal strokes

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34.1. Physiology of the spinal cord circulation

The physiology of the spinal cord circulation has much in common with the physiology of the cerebral circulation. Several factors participate in regulation of blood circulation: systemic blood pressure, blood gases, changes in vascular tone, and so on. As is the case for blood circulation in the brain, autoregulation is also characteristic of spinal blood circulation in response to fluctuations of systemic blood pressure: an abrupt increase in arterial blood pressure leads to an increase in vascular tone, and abrupt reduction of systemic blood pressure to its decrease, which is accompanied by vasodilatation. Kindt (1971) showed that autoregulation of spinal blood circulation in macaques is well preserved even if the spinal cord is separated from the brainstem. The mechanisms of autoregulation provide adequate spinal circulation under conditions of arterial blood pressure fluctuations from 45 to 180 mmHg. However, perfusion of the spinal cord is more significantly dependent upon systemic blood pressure. It was shown that a low peripheral vascular resistance, leading to aortic hypotension, diverts aortic outflow away from the spinal cord vessels, whereas in cases when peripheral vascular resistance is high in the lower extremities, aortic outflow is diverted toward the spinal circulation, increasing pressure and possibly perfusion as well.

Despite the established fact that blood oxygen and carbon dioxide (CO_2) content play a less significant role in regulation of the spinal circulation than of the cerebral circulation (Field et al., 1951; Klevtsov, 1968), similarities can generally be seen (Palleske, 1968; Skoromets et al., 2003): an increase in the partial pressure of CO_2 leads to an increase in spinal circulation due to vasodilatation; reduction of partial pressure of CO_2 leads to the opposite effects. Hypoxia results in reduction of the spinal circulation, with motor neurons being the most sensitive to anoxia.

A local increase in circulation develops within the zone of functional activity of spinal neurons and does not depend upon systemic arterial pressure. The clinical significance of this phenomenon is that in some cases, when the spinal circulation is sufficient under resting conditions, it can be exhausted under conditions of functional exertion, and relative ischemia develops, especially involving the spinal gray matter. A clinical example is so-called myelogenic intermittent claudication, which was described by Dejerine in 1906 (Zulch and Kurth-Schumacher, 1970).

Arteriovenous anastomoses (or shunts) between the anterior median spinal artery and the anterior medial spinal vein, which are usually found at the level of enlargements of the spinal cord, play a considerable role in the function of the spinal circulation. At rest, when functional activity of spinal neurons is minimal, part of the arterial blood is delivered through these anastomoses directly into the veins. When neurons of enlargements of the spinal cord are activated the requirement for spinal cord blood flow increases, anastomoses are closed by reflex action, and all flowing arterial blood is delivered into the spinal cord matter. The blood flow is slower through the spinal cord than through the brain and has a rate of 1.63 ml/g/min in gray matter and 0.14 ml/g/min in white matter. The average arterial pressure in the spinal cord is substantially lower than that in the aorta.

Electrical stimulation of different regions of the peripheral nervous system produces heterogeneous changes; in the brain as well as in the spinal cord, excitation of sympathetic autonomic nerve fibers leads to an

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increase in vascular tone, whereas excitation of the vagal nerve and of afferent fibers of the ischiatic nerve causes its reduction. It is important to note that tone fluctuations are not connected with changes in systemic blood pressure. The extent of vascular tone changes in spinal vessels is less than in cerebral ones, which is probably connected with higher vascular tone in spinal vessels under normal conditions. The peculiarities of vasomotor regulation of the spinal circulation include the relatively weak vasoconstricting and the relatively prominent vasodilating effects. Meanwhile, electrical stimulation of the cervical sympathetic trunk leads to an increase in the vascular tone in spinal vessels. Acute experimental injury of the spinal cord with irritation of the cervical sympathetic trunk is accompanied by spasms of the sulcal and the sulcal–commissural arteries leading to development of chronic insufficiency of blood circulation in their territories, which is clinically manifested by a post-traumatic progression of neurological signs (Koyanagi et al., 1993). Compression of the thoracic region of the spinal cord also leads to a vasoconstricting response with heart rate reduction due to stimulation of sympathetic nuclei at the level of T12 to L1. Neurological signs may progress after ischemia of the spinal cord under conditions of post-ischemic hypoglycemia (Hemmila et al., 1993), impairment of calcium channel function in spinal neurons (Danielisova and Chavko, 1994), and increase in glutamate and aspartate levels (Rokkas et al., 1994).

In some cases, spinal blood circulation may be redistributed from other streams of aortic circulation in response to changes in the vasomotor tone initiated by reflexes. An important reflex is the diving reflex, when liquid applied to the face or snout area triggers a reflex over the afferent limb of the trigeminal nerve; the response is initiated through the efferent limb of the vagal nerve and the splanchnic circulation induces bradycardia and peripheral vasoconstriction, with redistribution of blood to the brain and spinal cord.

Experimentally, it was shown that local blood circulation in spinal segments is reduced after chemical stimulation (with L-glutamate) of the rostral ventrolateral pressure zone of the brainstem (Maeda et al., 1992). A prominent vasoconstrictive effect in spinal vessels was observed after injection of somatostatin (Long et al., 1992). Hypotension of spinal blood circulation can be induced by injection of prostaglandin E_1. The latter is applied during surgery of tumors of the spinal cord to reduce bleeding (Abe et al., 1994).

34.2. Spinal cord infarction

Acute spinal cord ischemia syndrome (ASCIS) is rare, accounting for about 5–8% of all acute myelopathies and 1–2% of all vascular neurological pathologies (Sandson and Friedman, 1989; Nedeltchev et al., 2004). In rehabilitation centers for spinal cord injuries, infarctions constituted 4.2% of all admissions (Iseli et al., 1999).

34.2.1. Etiology

Ischemia and infarction of the spinal cord may develop at any age, but frequently affects people aged 41–60. The etiology of spinal infarctions is variable. The classification of obstructive arterial lesions most often responsible for spinal ischemia and infarction is presented in Table 34.1.

An obstructive lesion causing spinal cord ischemia can be situated anywhere from the aortic origin of the segmental arteries to the spinal arterioles. Compared with occlusive vascular disease of the brain, spinal cord vascular disease is not as common in clinical practice. Nevertheless, symptomatic aortospinal atherosclerosis does occur, and cord infarction, as well as transient ischemia with reversible neurological deficit, is recognized. Among patients with ASCIS, Nedeltchev et al. (2004) described atherosclerotic changes in the arteries supplying the spinal cord in 33% of cases; they believe an atherosclerotic origin of infarctions of the spinal cord is rarely diagnosed because spinal angiography is not a routine diagnostic examination.

One of the most prevalent causes is aortic pathology; there is a 3–5% risk of cord ischemia in aortic dissection and a 1–10% risk in aortic surgery (Connolly, 1998; Cunningham, 1998; Inamasu et al., 2000; Nedeltchev et al., 2004; Shinoyama et al., 2005). Spontaneous and traumatic dissections of the aorta may cause occlusion of the ostium of segmental arteries and hence lead to development of spinal cord infarction. Pressure applied to the lumbar aorta to arrest uterine hemorrhage or contrast medium introduced into the aorta near the ostium of a segmental artery during renal or lumbar aortography might also cause acute ischemia of the spinal cord.

A common causative factor of ASCIS (about 15–30%) is degenerative spine disease. Spondylotic vertebral spurs can compress spinal arteries and impair blood supply to the cord. Protrusion of a nucleus pulposus displaces the spinal cord posteriorly, stretching dentate ligaments that suspend the cord in the spinal canal. Squeezing of the spinal cord between the ligaments and the nucleus pulposus can cause venous congestion and spinal ischemia (Hughes and Brownell, 1964; Cates and Soriano, 1995; Skoromets et al., 2003; Nedeltchev et al., 2004; Ram et al., 2004; Shibuya et al., 2005).

Table 34.1

Classification of spinal strokes. Different criteria may underlie classification of spinal strokes

Causative factors
Obstructive arterial lesions:
Hereditary pathology: malformations (aneurysms): arterial, arteriovenous; hypoplasia; telangiectasia
Acquired pathology:
Atherosclerosis and its complications
Infectious arteritis (tuberculosis, syphilis etc.)
Collagen vascular disease (polyarteritis nodosa, systemic lupus erythematosus, rheumatism)
Sarcoidosis
Arteriopathies (toxic; endocrine such as diabetic; radiation-induced)
Embolism
Compressive lesions of vessels of the spinal cord in:
Vertebral diseases (fracture with dislocation of the spine, hyperextension injuries of the cervical spine, spondylosis, hereditary abnormalities of vertebrae, subluxations, intramedullary tumors)
Extramedullary compression (extramedullary tumors, meningeal pathology, extravertebral tumors and neoplasm-like pathologies, pregnancy)
Iatrogenic pathology (pressure applied to lumbar aorta to arrest uterine hemorrhage, complications of surgery of the abdominal and thoracic aorta, aortography, laminectomy, thoracoplasty, dorsolumbar sympathectomy, gastrectomy, esophagectomy, epidural anesthesia, lumbar puncture, chiropractic) manipulations, and others)
Impairment of systemic and local blood flow: myocardial infarction, abrupt fluctuations of arterial pressure (hypotension or hypertension), reflex impairment of vascular tone
Coagulopathy and hemorheologic disturbances
Origin and location of vascular lesions of the spinal cord
Origin: malformation, aneurysms (hereditary, acquired), occlusion or stenosis, compression; dissection; increased permeability of vessel walls, etc.
Location:
Aorta and its branches (subclavian, intercostal, vertebral, lumbar, sacral arteries)
Radicular–medullary arteries (anterior, posterior), including the great radicular–medullary artery of Adamkiewicz, the inferior additional radicular–medullary artery of Deproges–Gotteron
Anterior median and posterior spinal arteries, the perimedullary arteries, pial arteriolar plexus (“vasocorona”)
Intramedullary arteries (sulcal and sulco-comissural arteries)
Venous system (intramedullary and perimedullary veins of the spinal cord, radicular veins, vena cava superior and inferior)
Expanded vascular lesion of unidentified location
Type of spinal stroke
Spinal cord infarction (compression, embolismic, thrombotic, non-thrombotic)
Spinal cord hemorrhage (hematomyelia, spinal subarachnoid hemorrhage, epidural and subdural hemorrhage)
Location of lesion of the spinal cord
Along longitudinal axis of spinal cord: myeolbulbar, cervical enlargement, superior thoracic, inferior thoracic, lumbosacral enlargement, conus medullaris, cauda equina)
Along transversal section of spinal cord: transversal (total), lesion of ventral two thirds, of anterior horns, of central medullary zone, of dorsal third, of half (right or left)
Features of clinical syndromes
Motor loss (peripheral, central of mixed paresis or palsy)
Sensory loss (pain: local, radicular, segmental, below lesion; hypesthesia/anesthesia: radicular, segmental, below the lesion, total)
Pelvic sphincters impairment (urinary incontinence or retention, imperative urges, ischuria paradoxa, constipation)
Trophic disturbances (bedsores, hyperkeratosis, angiodystonia, etc.)
Functional outcome
No disability
Disability of different levels

Injuries exert multiple influences on the spinal cord, frequently leading to secondary vascular damage of the spinal cord due to compression of radicular–medullary and spinal arteries, traumatic dissection of arteries, reflex spasm of vessels, and impairment of autoregulation.

There is a long list of rather rare causes of obstructive arterial lesions associated with ASCIS, including syphilitic or tuberculous arteritis, arteriopathies of different origin (diabetes mellitus, radiation, collagen vascular disease, sarcoidosis), cardiac and other types of embolism, iatrogenic myelopathy, and coagulopathy (see Table 34.1).

Fibrocartilaginous embolism is a rare cause of spinal cord infarction, usually occurring after minor trauma without major bony lesions (Han et al., 2004; Raghavan et al., 2004). There is evidence that the embolus originates from the intervertebral disk, but the mechanism whereby disk fragments enter the spinal vessels is not well understood. It is postulated that an acute vertical disk herniation of the nucleus pulposus material can lead to spinal cord infarction by a retrograde embolism to the central artery. An increased intradiskal pressure resulting from axial loading of the vertebral column with a concomitant Valsalva maneuver is thought to be the initiating event for the embolus.

In rare cases, spinal infarctions occur as complications of laminectomy, thoracoplasty, dorsolumbar sympathectomy, gastrectomy, esophagectomy, coronary and vertebral angiography, or consequences of inadvertent epidural anesthesia, lumbar puncture, and chiropractic manipulations (Aramburu et al., 2000; Pathak et al., 2000).

Spinal infarction can be a result of radiation for bronchogenic carcinoma (at the level of thoracic segments) and for malignant tumors of the thyroid gland, cervical lymphatic nodes, and upper respiratory tract (at the level of cervical enlargement and superior thoracic segments). In these cases, radiation vasculopathy of the small intramedullary arteries usually develops. Spinal infarctions require differentiations with intramedullary metastases.

A very high overall frequency of ischemic lesions of the spinal cord occur with global ischemia after cardiac arrest or a severe sustained episode of arterial hypotension (in 46%; Duggal and Lach, 2002). Under these conditions, development of ischemic necrosis in borderzones between major arterial territories is well documented in clinical and experimental studies. Historically, the literature has supported the notion of a spinal cord "watershed zone" of ischemic vulnerability centered at the mid-thoracic level (Bartsch and Hopf, 1963; Garland et al., 1966; Marcus et al., 1977; Garcia, 1988; Sliwa and Maclean, 1992). This assumption was based largely on anatomic studies and case reports describing the relative hypovascularity of the region from T4 to T8. However, modern investigations indicate a greater vulnerability of the lower thoracic and lumbosacral neurons to ischemia (Imaizumi et al., 1994; Cheshire et al., 1996; Idali et al., 1996; Duggal and Lach, 2002) that can be most likely connected with greater metabolic demands of the gray matter at this level of the spinal cord. In 7–36% of cases, no primary cause can be discovered (cryptogenic infarction of the spinal cord) (Nedeltchev et al., 2004). Ischemia in the radicular–medullary territories may develop not only due to occlusion of the trunk, but also due to that of its source (the intercostals artery or aorta), if consistent collateral flow is not formed in time.

Obstructive lesions of different arteries are associated with different causative factors. Frequent etiological factors for obstructive lesion of the aorta are dissection, atherosclerosis, atherosclerotic or syphilitic aneurysm, Takayasu's disease, complications of surgery of the abdominal and thoracic aorta, and aortography. The common causative factors for obstructive lesion of vertebral arteries are fracture with dislocation of the spine, hyperextension injuries of the cervical spine, cervical spondylosis, and vertebral arteriography; for intercostal artery lesion—post-operative complications (thoracoplasty, dorsolumbar sympathectomy) and coarctation of the aorta; for medullary artery lesion—extramedullar occlusion by tumors or tuberculosis, ligation during surgery for replacement of thoracolumbar aorta, and complication of aortic arteriography. Obstructive lesion of spinal arteries can be caused by mechanical compression, diabetic arteriopathy, syphilitic arteritis, and rarely by atherosclerosis. Small intramedullary vessels can be occluded as a result of arteritis or arteriopathy (collagen diseases, endarteritis obliterans, syphilis, tuberculosis, sarcoidosis), embolism of different genesis, chronic adhesive arachnoiditis, as well as coagulopathy and a reflexive peripheral vasoconstriction.

34.2.2. Clinical features

Infarction of the spinal cord develops acutely in the majority of cases. Symptoms develop within several minutes to hours, depending upon the rate of occlusion, accompanying reflex factors, and activation of compensatory mechanisms. Infarction of the spinal cord frequently occurs on the background of warning signs—those clinical features that preceded the onset of the disease. Some of the precursors are not manifestations of blood supply impairment but reflect a causative factor that determines the development of spinal

ischemia. As in corresponding cerebral disorders, recent and remote precursors are of great diagnostic significance. Recent precursors, that appear not long before stroke onset, are back pain, which may radiate in radicular fashion at the involved level, as well as its combination with several paresthesias (numbness, burning, prickles, sense of electrical current) in limbs and trunk.

Also, such motor signs as transient limb paresis may be precursors that frequently appear several days or weeks before the development of spinal ischemic stroke (myelogenic intermittent claudication) (Zulch and Kurth-Schumacher, 1970). Such an intermittent limb weakness may result from transient spinal ischemia that is rapidly compensated for by collateral flow. Transient disturbances may be single or multiple as it is inherent in myelogenic intermittent claudication as well as for intermittent "drop attacks," which occur in cervical cord ischemia.

The diagnosis of intermittent ischemia of the thoracic or lumbar parts of the cord should be considered when weakness of the lower limbs is precipitated by physical effort, particularly if strength is rapidly restored by rest, and accompanied by no pain and no changes in pedal pulses. If the causative lesion is in the abdominal aorta, exercise may also lead to pain in the hips (because of ischemia of the gluteal muscles) and dysuria, pollakiuria, and impotence (Leriche's syndrome).

If back pain precedes or accompanies the onset of acute spinal ischemia, it usually ceases after weakness or anesthesia appear. Frequently, after the onset of spinal stroke, fasciculations in muscles and trembling of extremities may appear. This phenomenon has been described in animals developing spinal stroke after clipping of the aorta. Severe spinal infarction is usually accompanied by reflex cerebral signs (syncopes, headache, nausea, general weakness). However, all these phenomena rapidly regress, whereas spinal signs worsen.

Individual variability of spinal vascular anatomy precludes verification of the location of the occluding process with precision according to clinical findings. Clinical signs are determined by the location of infarctions in relation to the transverse section of the spinal cord. However, spinal blood supply is more frequently impaired at an extramedullary site, where arteries enter the spinal channel, or on the extravertebral level. Ischemia develops in the distal areas of the occluded artery territory, which can be far from the location of the occluding process.

The origin of focal neurological signs is always determined by the location and the distribution of the infarction along the longitudinal and the transverse axis of the spinal cord. In some cases only gray matter is affected; in others, gray and white matter are affected simultaneously. Infarction may occupy the ventral or the dorsal part of the spinal cord (the anterior median or posterior spinal artery territory). Either half of the transverse section of the spinal cord is affected, or the whole transverse section or the centromedullary zone will be.

Spinal signs include several variants of quadri-, para-, hemi-, and monoparesis; sensory loss, corresponding to the infarction topography; pelvis sphincter impairment (urinary incontinence or retention, imperative urges, ischuria paradoxa, constipation); trophic (bedsores, hyperkeratosis, angiodystonia, etc.) and autonomic (vasomotor, sweat, and pilomotor) disturbances. Motor signs are the most persistent signs of spinal cord infarction (Pelser and van Gijn, 1993).

In the differential diagnosis one should consider myelitis, arachnoiditis, hematomyelia, intra- and extravertebral tumors, multiple sclerosis, and so on. Of course, of significant diagnostic value are different additional investigations, such as emergency magnetic resonance (MR) imaging and/or computed tomography (CT) supplemented with myelography (with air and contrast agents) as necessary. Roentgenographic studies and CT may show the collapse or erosion of a vertebra, whereas MR imaging may show an abnormality of the cord itself. Also of diagnostic importance are the investigation of the dynamics of cerebrospinal fluid, its cellular and chemical composition, electromyography, and selective spinal angiography. Angiography is seldom used in the investigation of the spinal cord. It is extremely difficult technically to obtain selective filling of the spinal cord vessels with the contrast medium. It is also difficult to analyze the angiograms due to the inevitable escape of the contrast medium into the extravertebral vascular network. The pictures of spinal cord infarctions in experiments on animals are scantily elucidated in the literature from the anatomical and histological points of view.

34.2.3. Anterior spinal artery syndromes

Infarcts in the territory of the anterior spinal artery occur in 85% of cases of acute spinal cord ischemia. They vary in their location in relation to the level of spinal cord segments and in the transverse plane (within limited area of the anterior two-thirds of the spinal cord); their longitudinal extension may be different. This explains the variability of the clinical features.

34.2.3.1. Ventral spinal cord transection syndrome

A syndrome of the lesion of the ventral part of the spinal cord transverse section may develop when the

anterior median spinal artery itself or its intramedullary branches, or the trunk of the anterior radicular–medullary artery, including that of Adamkiewicz, are occluded, as well as in cases of the intercostals, lumbar, sacral arteries, and aorta pathology (Kume et al., 1992; Siroky et al., 1992; Baba et al., 1993).

This syndrome occurs in 67% of cases of acute spinal cord ischemia and is associated with a more severe neurological deficit than with Brown–Sequard syndrome and a worse prognosis (Nedeltchev et al., 2004). The syndrome is characterized by a lesion of the ventral two-thirds of the spinal cord, that is manifested with an acute flaccid paralysis of all or only the lower extremities (depending on the level of ischemic lesion) and loss of pain and temperature sensations. Sphincter control is lost immediately, and there is often reflex ileus and abdominal distention secondary to acute interruption of sympathetic pathways. Because the posterior columns are not involved, vibratory sensation and proprioception is preserved. Loss of spinothalamic function with preservation of posterior column function is the distinguishing characteristic of this syndrome.

The initial flaccidity and loss of tendon reflexes are associated with spinal shock and are gradually replaced by spasticity in all muscles below the level of the lesion, with brisk tendon reflexes and extensor plantar responses. At the same time, development of necrosis of the anterior horn cells causes remaining flaccid paralysis in the muscles at the level of the occlusion; they then become atrophic. Infarction may occupy both halves of the ventral zone of the spinal cord more or less symmetrically, but may affect only half of its transverse section when Brown–Sequard syndrome develops.

34.2.3.2. Brown–Sequard syndrome

The clinical picture of Brown–Sequard syndrome may develop when the sulcal and sulcal–commissural arteries from one side of the transverse section of the spinal cord are occluded, as well as when the anterior median spinal artery and its sources are occluded. The unilateral distribution of the sulcal arteries is rudimentary and is preserved from the period of embryonic development when each of two corresponding longitudinal anterolateral vascular tracts supplied the homologous part of the spinal cord. When the sulcal arteries arise from the areas of duplication (“insulas”) of the anterior median spinal artery, each branch from one and the other side of an insula goes to the homologous part of the spinal cord. The unilateral character of the spinal cord blood supply can explain the possibility of development of Brown–Sequard syndrome under conditions of spinal blood supply impairment. Typically, Brown–Sequard syndrome develops at the level of the cervical segments, where areas of duplication of the anterior median spinal artery are more frequently seen (Baumgartner and Waespe, 1992; Milandre et al., 1993; Goldsmith et al., 1998). The important feature of Brown–Sequard syndrome of vascular origin is preserved perception of vibration, position, and light touch that is explained by the location of ischemia in the anterior median spinal artery territory.

34.2.3.3. Anterior horn syndrome

Ischemic lesions may locate predominantly in the anterior horns of the spinal cord. A selective lesion of motor neurons is explained by higher sensitivity of the gray matter to ischemia as compared with white matter. The *anterior horn syndrome* is caused by occlusion of the anterior median spinal artery itself and its intramedullary branches (Skinhoj, 1954; Garcin, 1964). A clinical picture resembling poliomyelitis is characteristic: flaccid palsies of legs without sensory loss. A stroke-like course in the setting of precursor events, frequent association with changes in systemic blood circulation, and absence of infectious signs differentiate it clinically from poliomyelitis.

34.2.3.4. Centromedullary syndrome

Infarctions may develop in the central zone of the transverse section of the spinal cord, around the central channel (Zulch, 1954; Hogan and Romanul, 1966). Development of centromedullary infarction is described under conditions of cervical spine injury, syphilitic arteritis, and operations for prosthetic appliance of the aorta (Fujigaki et al., 1992; Wada et al., 1992; Weimann et al., 1992; Pullicino, 1994), compression, and occlusions of the segmental and radicular–medullary arteries (Skoromets et al., 2003). Such a location of ischemia is manifested by flaccid paralysis in trunk muscles and extremities, as well as by the segmental dissociated loss of pain and temperature sensations. The lesion usually does not involve the posterior and lateral columns. Frequently, irregular and asymmetrical lesions of anterior horn motor neurons appear in centromedullary infarction. As a result, one group of muscles is affected on one limb, and another group on another limb (Skoromets et al., 2003), which causes marked gait disturbances.

34.2.4. Posterior spinal artery syndrome

Infarcts in the territories of the posterior spinal arteries are rare. Nedeltchev et al. (2004) revealed posterior spinal artery infarcts in 3% of all acute spinal cord ischemia syndromes. Their causes include syphilitic

arteritis (Skoromets et al., 2003), cholesterol emboli from atheromatous aortic plaques (Perier et al., 1961), intrathecal injection of phenol (Hughes, 1970), vertebral artery dissection (Gutowski et al., 1992), and plasmacytoma (Schott et al., 1959). In many cases their pathogenesis remains unknown (Kaneki et al., 1994).

The majority of posterior spinal artery infarcts occur at the thoracolumbar level (Perier et al., 1961; Kaneki et al., 1994) but they have also been observed at the thoracic (Schott et al., 1959; Garcin, 1964; Hughes, 1970) and cervical (Samson et al., 1963; Gutowski et al., 1992; Fukuda and Kitani, 1994) levels. Longitudinal extension of these infarcts averaged two vertebral segments, but their span can range from one to six segments (Garcin, 1964; Kaneki et al., 1994) (Fig. 34.1).

The more extensive lesions involve the posterior portion of the lateral column, the posterior column, and the posterior gray horns, either bilaterally or unilaterally. Selective lesions of the posterior gray horn and lateral and posterior column have been described. The anastamoses of the pial network are so extensive that any one, or even several, of the ramifications can be occluded without the production of a clinical deficit.

Clinical features are variable and include loss of vibratory sensation and proprioception due to damage of the posterior column, suspended global anesthesia, segmental tendon areflexia due to posterior horn involvement, and paresis below the level at which the posterior portion of the lateral column containing the crossed corticospinal tract is affected.

34.2.5. Complete spinal cord transection syndrome

Complete spinal cord transection syndrome may develop after occlusion of arteries on different levels, distant from the spinal cord (sources) as well as the intramedullary arteries. Necrosis of the whole transverse section of the spinal cord develops under conditions of simultaneous interruption of blood supply in the anterior median and posterior spinal artery territories or in cases when the anterior radicular–medullary artery participates in formation of the anterior as well as posterior longitudinal arterial tracts.

Ischemia reaches the maximal extent and occupies all the transverse section of the spinal cord at the level where the radicular–medullary artery enters it. Above and below this level compensatory blood supply develops, and necrosis appears to be more restricted, occupying predominantly the central areas of the gray matter ("pencil syndrome"; Zulch, 1954). The clinical picture of complete spinal cord transection syndrome is represented by quadri- or lower paraplegia, anesthesia of all sensation modalities below the lesion, disturbances of pelvic sphincters, and development of autonomic and trophic disturbances.

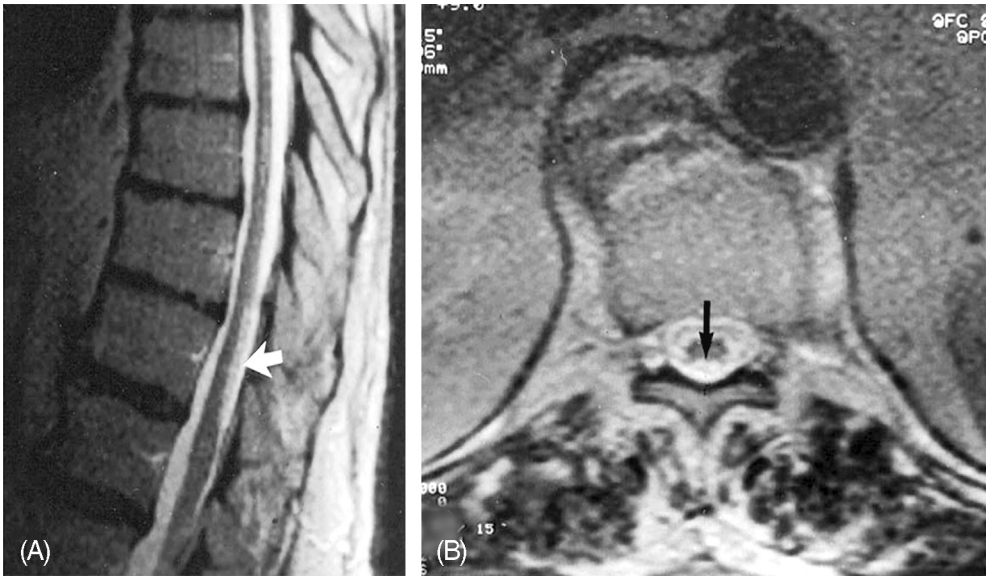

Fig. 34.1. Infarction in the territory of the posterior spinal artery. (A) Sagittal T2-weighted (4500/120/6) fast spin-echo image obtained 4 months after endovascular therapy shows sharply defined elongated high signal intensity of the posterior spinal cord (arrow) at T10–11. (B) Axial T2-weighted (5000/120/6) fast spin-echo images show sharply defined signal changes (arrow) involving the posterior columns at T11. Reproduced from Mascalchi et al., 1998 with permission. © American Society of Neuroradiology.

34.2.6. Clinical peculiarities in relation to location of ischemia along the longitudinal axis of the spinal cord

Clinical peculiarities of spinal infarctions strongly depend on the type of spinal vascularization that is determined by the number and the level of medullary arteries that enter the spinal cord. Two extreme varieties of spinal blood supply can be distinguished in relation to the number of the anterior radicular–medullary arteries, this number ranges from one to five for the thoraco-lumbo-sacral part of the spinal cord (inferior arterial region): the magistral (paucisegmental) type and the scattered (plurisegmental, polytrunkal) type (Jellinger, 1966; Skoromets et al., 2003) (Fig. 34.2).

Several variants can be related to the magistral type of spinal blood supply (Skoromets et al., 2003): the first—when all the segments below the T2 level are supplied by a single artery of Adamkiewicz (Fig. 34.2A); the second—beside the artery of Adamkiewicz, there is an additional inferior medullary artery that goes together with the L5 or S1 roots (Fig. 34.2B); the third—beside the artery of Adamkiewicz, there is the additional superior medullary artery that accompanies one of the thoracic roots from T3 to T6 (Fig. 34.2C). In the scattered (plurisegmental, polytrunkal) type of spinal blood supply, three or more medullary arteries supply all the spinal segments below the level of T2 (Fig. 34.2D).

According to Skoromets et al. (2003) the first variant of the magistral type of spinal blood supply is found in 20.8% of cases, the second in 16.7% of cases, and the third in 15.2% of cases; the plurisegmental type is seen in 47.2% of cases. If the patients have the magistral type of spinal vascularization, the compensatory capacity of collateral blood flow is restricted.

34.2.6.1. Ischemia of superior cervical segments

Ischemia of the superior cervical segments frequently develops in atherosclerosis of the vertebral arteries, their spondylitic compression or dissection. Typically, it is accompanied by ischemia of the brainstem, cerebellum, sometimes the occipital and temporal lobes, and deep structures of the cerebral hemispheres. Transient ischemic attacks in the vertebral and basilar artery territory are commonly seen and have a varying spectrum of clinical manifestations.

Unilateral intracranial anterior spinal ramus syndrome causes ventral medullary syndrome, reflecting localization of infarction in the homolateral pyramid, the medial lemniscus, and the hypoglossal nucleus and nerve. Clinical features include contralateral spastic hemiparesis, ipsilateral loss of vibratory sensation and

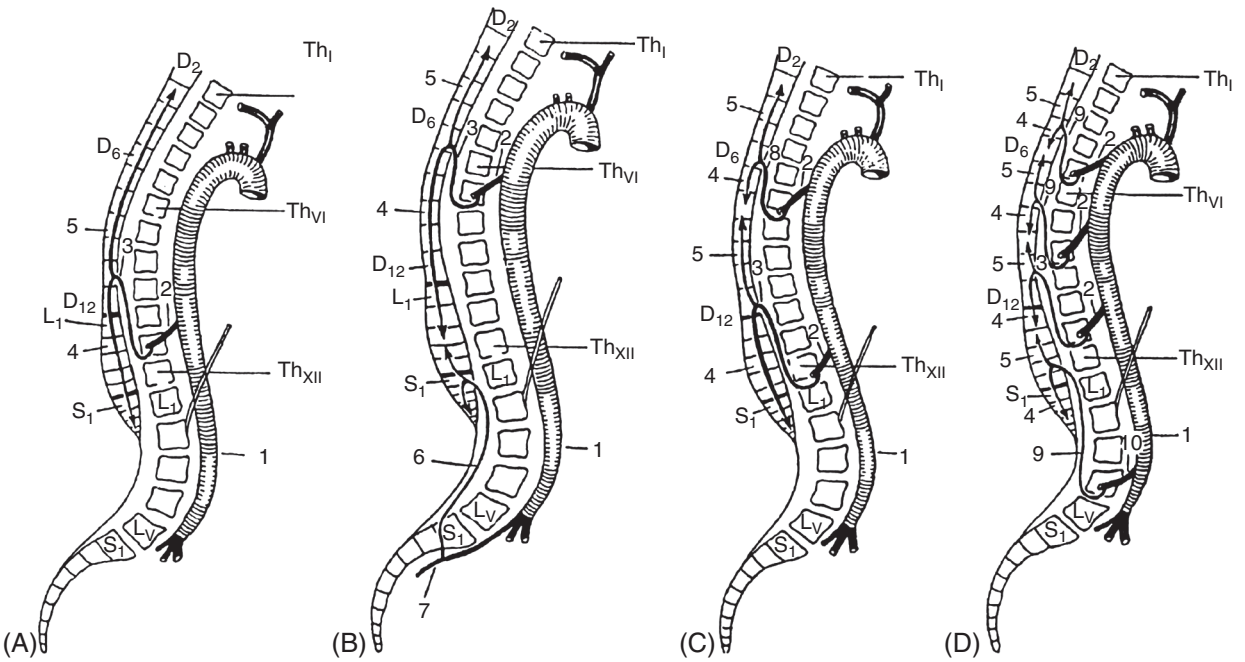

Fig. 34.2. Variants of thoraco-lumbar-sacral spinal cord segments vascularization. Spinal blood supply variants: magistral (A–C) and scattered (D) types. 1 = aorta; 2 = intercostal arteries; 3 = great radicular–medullary artery of Adamkiewicz; 4 = anterior radicular–medullary artery, descending branch; 5 = anterior radicular–medullary artery, ascending branch; 6 = inferior additional radicular–medullary artery; 7 = median sacral artery; 8 = superior additional radicular–medullary artery; 9 = radicular–medullary artery; 10 = lumbal artery.

proprioception, flaccid paresis, and atrophy of the tongue. Perception of pain and temperature is preserved.

Bilateral intracranial anterior spinal ramus syndrome is manifested with tetraplegia and loss of vibration and position sense in all four limbs.

Infarction in the anterior spinal artery territory at the level of the superior cervical segments can be maximally manifested by spastic quadriparesis, anesthesia of pain and temperature sensations below the lesion, and loss of sphincter control. Vibratory sensation and proprioception are intact.

Variants of restricted central medullary ischemia are possible with development of centromedullary syringomyelia-like syndrome that is manifested by segmental dissociation anesthesia of pain and temperature sensations in C1–C3 dermatomes, as well as by the lesion of anterior horns of C1–C3 segments with the development of hanging head syndrome.

In some cases ischemia, which is caused by a spondylogenic process, may be located within the anterior horn over one or two segments of the spinal cord, and it may be distributed into the spinal roots. In this case, a typical clinical picture is seen (sporadic Parsonage–Turner syndrome): precursors such as intense pain in the cervical spine that radiates into the upper limb girdle, then flaccid paresis of proximal muscles of the homolateral upper extremity with rapid development of atrophy. When paresis appears the pain usually disappears or markedly reduces.

One rare observation is symmetrical infarction within the ventral two-thirds of the cervical spinal cord ("snake-eye" conformation) due to spontaneous bilateral dissection of vertebral arteries with nearly total proximal stenosis and low blood flow in the basilar artery (Hundsberger et al., 1998; Fig. 34.3). Occlusion of these branches causes hypoperfusion in the territory of the anterior spinal artery, which results in development of bilateral watershed infarctions. Clinical features of such a lesion include the sudden onset of bilateral neck pain radiating into both arms, progressive unsteadiness of gait, weakness of all the extremities (or hemiparesis) with loss of deep tendon reflexes in acute phase, bilateral loss of pain and temperature sense below the level of infarction, acute urinary retention, and fecal incontinence. Cranial nerve functions are normal, and MRI of the cerebellum and brainstem is also normal.

34.2.6.2. Ischemia of the cervical enlargement of the spinal cord

In cases of magistral vascularization of the cervical region of the spinal cord, transient and persistent myeloischemia may develop due to insufficiency of the blood supply in a large radicular–medullary artery. Frequently this artery is a branch of the deep cervical artery and approaches the spinal cord together with one of the roots from C5 to C7/C8; less frequently it is a branch of the vertebral artery.

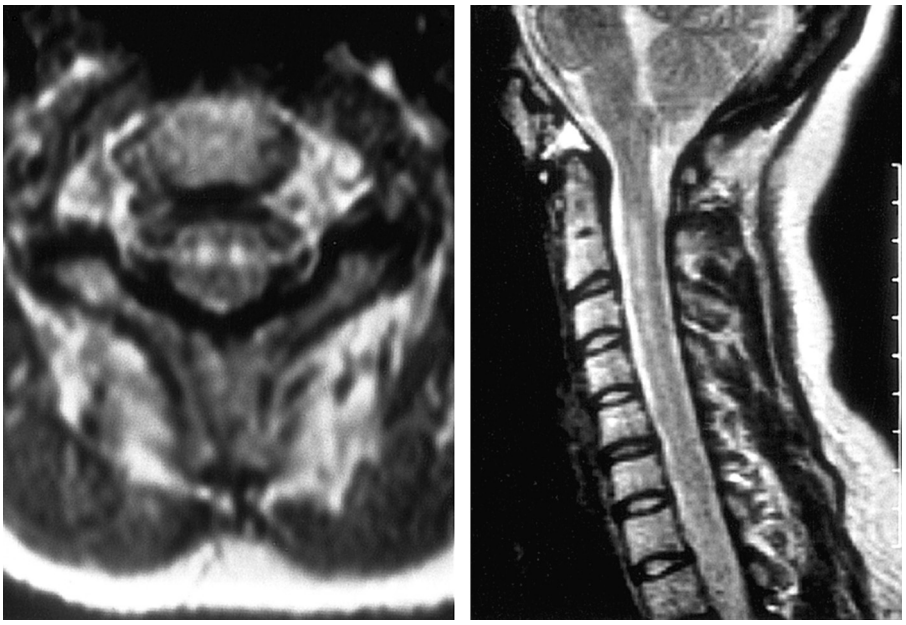

Fig. 34.3. Symmetrical infarction within the ventral two thirds of cervical spinal cord. Cervical MR scan 1 day after admission. (Left) T2-weighted magnetic resonance axial scan at C3 level showing bilateral cervical spinal cord hyperintensities ("snake-eye" conformation). (Right) Sagittal MR scan visualizes expansion of this lesion from C2 to C5 vertebral levels. Reproduced from Hundsberger et al. (1998) with permission from Lippincott Williams & Wilkins.

Total myeloischemia of the cervical enlargement of the spinal cord is manifested by upper flaccid paraparesis, lower spastic paraparesis, segmental anesthesia, anesthesia below the lesion, and central impairment of pelvic sphincters. Typically, it is seen in cases of protrusion of a nucleus pulposus at the cervical level, fracture with dislocation, and flexion-and-extension injuries of the cervical spine (whiplash injuries).

More frequently reserve capacities exist at the level of the cervical enlargement to perform compensatory blood flow through both branches of the vertebral arteries and adjacent radicular–medullary arteries. As a result, a local restricted infarction develops within the area of anterior horns or the centromedullary zone. Acute brachial diplegia with normal findings of the legs, "man-in-the barrel" (MIB) syndrome, has also been described as a result of unilateral vertebral artery dissection (Berg et al., 1998). Cases of ischemia in the posterior spinal artery territory are extremely rare. They manifested in posterior column syndrome: paresthesias below the lesion, sensitive ataxia, and moderate pyramid deficiency.

34.2.6.3. Ischemia of the superior thoracic segments of the spinal cord

Myeloischemia of the superior thoracic segments of the spinal cord may develop when the bloodstream is blocked in the superior additional radicular–medullary artery, which accompanies one of the roots from T1 to T6, or by the mechanism of ischemia of the watershed boundary zone between the superior and inferior spinal arterial regions. It often leads to complete spinal transection syndrome, as the posterior radicular–medullary arteries are absent at the level of the superior thoracic segments in more than 10% of cases (Lazorthes et al., 1966), and the anterior radicular–medullary artery takes part in formation of the anterior as well as posterior longitudinal arterial tracts.

Paraparesis, anesthesia of all sensation modalities below the T1–T2 dermatomes, and pelvic sphincter impairment, frequently as urinary and fecal retention, develop acutely. In the first few days after stroke, knee and Achilles reflexes disappear (spinal diathesis), but extensor plantar responses may be elicited. Then the lower extremity paraparesis develops additional features, spasticity, and hyper-reflexia in lower extremities.

34.2.6.4. Syndrome of occlusion of the artery of Adamkiewicz

The level where the artery of Adamkiewicz enters the spinal cord varies greatly—from the thoracic T5 up to the lumbar L5 segment of the spinal cord. In more than 70% of cases the artery of Adamkiewicz enters the spinal cord at the level of the thoracic segments, and in more than 80% of cases it does so from the left side (Rodriguez-Baeza et al., 1991; Skoromets et al., 2003). In cases of superior entrance of the artery of Adamkiewicz (T8–T10), it supplies all the inferior part of the thoracic and the whole lumbosacral region of the spinal cord (Corbin, 1961a). And in more than 35% of cases the inferior region of the spinal cord (below T4–T6) is supplied only by the single artery of Adamkiewicz (Corbin, 1961a,b; Skoromets et al., 2003).

Common reasons why the bloodstream through the artery of Adamkiewicz stops are compression of the artery itself at the level where it enters the spinal cord (protrusion of a nucleus pulposus, tumor), its atherosclerotic occlusion, as well as compression and occlusion of the proximal adducing arteries that form the artery of Adamkiewicz (the aorta itself and its branches).

In patients with the magistral type of spinal vascularization, the insufficiency of blood flow through the artery of Adamkiewicz may lead to spinal cord ischemia—from T4–T6 segments to conus (territory of the aorta), which cannot be compensated for by the collateral flow, and that causes development of *expanded infarction of the whole inferior half of the spinal cord*.

When the additional inferior radicular–medullary arteries accompanying the lumbar or sacral roots are presented, in cases of the plurisegmental type of blood supply, the zone of myeloischemia in the territory of artery of Adamkiewicz is far more restricted within the longitudinal axis due to more powerful capacities of the collateral flow.

Earlier the syndrome of occlusion of the artery of Adamkiewicz was considered equal to the ventral spinal cord transection syndrome, as the artery of Adamkiewicz frequently only approaches the anterior surface of the spinal cord while its branch, which passes together with the posterior root, is rudimentary or absent. However, sometimes both the anterior and posterior medullary branches of artery of Adamkiewicz take part in spinal blood supply; in these cases occlusion of the artery may cause complete spinal cord transection syndrome.

In rare cases the insufficiency of blood flow through the artery of Adamkiewicz may lead to development of Brown–Sequard syndrome. This is usually due to the presence of duplication regions of the anterior spinal artery, which is a branch of the artery of Adamkiewicz, and due to the unilateral character of the spinal cord blood supply through the sulcal arteries.

The level of a segmental lesion of the spinal cord under conditions of occlusion of the artery of Adamkiewicz varies greatly due to individual peculiarities

of spinal vascular anatomy (in particular, it depends on the level where the artery enters the spinal cord, on what type of spinal vascularization is presented—magistral or plurisegmental, and on the capacities of collateral flow).

34.2.6.5. Limited ischemia of the thoracic region of the spinal cord

Restricted infarctions of the thoracic region of the spinal cord usually develop in patients with the plurisegmental type of spinal blood supply. They are usually of secondary extravascular origin: due to compression of arteries, supplying the spinal cord, by metastases of internal viscera tumors, by spinal epiduritis, or by protrusion of a nucleus pulposus. However, they may develop due to primary lesion of walls of main arteries of the thoracic cavity (for instance, atherosclerosis of the aorta and its intercostal branches) or radicular–medullary arteries and their branches. The clinical picture is manifested by syndromes of complete or partial lesion of the spinal cord at the level of one or several thoracic segments.

34.2.6.6. Limited ischemia of the lumbosacral region of the spinal cord

Partial infarctions of the lumbosacral regions of the spinal cord do frequently develop in the segments of epiconus and conus in cases of the plurisegmental type of spinal vascularization. They may be caused by compression of one of the radicular arteries at the level where it enters the vertebral channel or by a herniation of an intervertebral disk. In rare cases, limited lumbosacral infarctions may be a complication of inadvertent epidural anesthesia, lumbar puncture, or chiropractic manipulations, as well as a manifestation of primary or secondary pathology of the abdominal aorta and its branches.

Infarctions of the lumbosacral region are always characterized by flaccid paresis (or plegia) of the lower extremities (in contrast to spinal infarctions of other locations) with reduction of knee and Achilles reflexes, segmental anesthesia, and anesthesia below the level of T12–L1, pelvic sphincter impairment, and massive trophic disturbances of skin (bedsores on sacrum, buttocks, and heels).

34.3. Spinal hemorrhage

According to the data presented in DePlagne's doctoral dissertation thesis (1961), the first case of spinal hematoma was reported in Duverney's manuscript in 1682. The first case that was clinically diagnosed and subsequently confirmed with autopsy was reported by Jackson in 1869 (Jellinger, 1975).

Spinal hemorrhages include bleeding into the epidural, subdural, or subarachnoid space, or to the spinal cord itself. In a review of 613 spinal hematomas published between 1826 and 1996, Kreppel et al. (2003) reported that 75% were epidural, 15.7% subarachnoid, and 4% subdural. The first symptom is usually acute pain. The location of the pain usually reflects the region of bleeding in the spinal axis. Neurological course may vary according to the severity, location, and the etiological causes of the bleeding as acute, subacute, or chronically evolving (Boyd and Pear, 1972).

The incidence of spinal hemorrhages is very low. According to the literature spinal hemorrhage occurs more frequently in males (Wisoff, 1996). In their literature survey, Kreppel et al. (2003) found that in a total number of 605 cases of spinal hemorrhages, the male to female ratio was 2:1. The ratio was similar for those with epidural and subarachnoid hemorrhage.

Spinal hemorrhage may occur without any identifiable cause or during strenuous physical activities such as coughing or during micturition. Except for major spinal trauma, other leading causes of spinal hemorrhage include the use of anticoagulant agents (Heppner et al., 2004), bleeding diathesis, spinal tumors, arteriovenous malformations, lumbar puncture, and spinal and epidural anesthesia (Moen et al., 2004). Kreppel et al. (2003) found the largest group (38%) composed of patients in whom no cause could be defined, or those occurring spontaneously during daily activity. Hemorrhages related to anticoagulant treatment or coagulopathies (22.5%), vascular malformations (9%), and spinal interventions represent other etiologies. Idiopathic and spontaneous hemorrhages were the leading cause in all age groups.

Although frequently reported as a complication in isolated cases (Schwander and Bachmann, 1991), according to data extracted from a larger series the calculated incidence of spinal hemorrhage due to spinal and epidural interventions is less than 1 in 220,000 and 1 in 150,000, respectively (Horlocker, 2004). The Second ASRA Consensus Conference on Neuraxial Anesthesia and Anticoagulation concluded that antiplatelet agents by themselves do not result in additional risk for spinal hematoma during epidural or spinal anesthesia (Horlocker et al., 2003). It seems hard to believe that anticoagulation by itself might cause spinal hemorrhage when the vast number of anticoagulated patients is considered (Bruyn and Bosma, 1976). Conversely, documented hemorrhagic complications of the central nervous system in large trials with anticoagulants almost always affect the brain (ASPECT Research Group, 1994; Levine et al., 2001). Hypertension is also reported to be among the

causes of spinal hemorrhage; however, there is not sufficient evidence to state what would cause spinal hemorrhage per se (Bruyn and Bosma, 1976; Groen and Ponssen, 1990).

34.3.1. Intramedullary hemorrhage

Bleeding into the spinal cord tissue represents a small group among spinal hemorrhages (Fig. 34.4). As seen in other types of spinal hemorrhages, bleeding may present with regional pain followed by acutely or subacutely evolving signs of transverse medullary syndrome. If blood enters the subarachnoid space, meningeal irritation signs may develop.

Excluding trauma, hematomyelia can be observed with intramedullary tumors (Yu et al., 1994), intradural arteriovenous malformations (Yasargil, 1976) and in the presence of coagulopathies or anticoagulant medications (Zeidman and Olivi, 1993; Pullarkat et al., 2000). Berenstein et al. (2004) emphasized the difficulty of determining the true incidence of hematomyelia in spinal intradural arteriovenous malformations

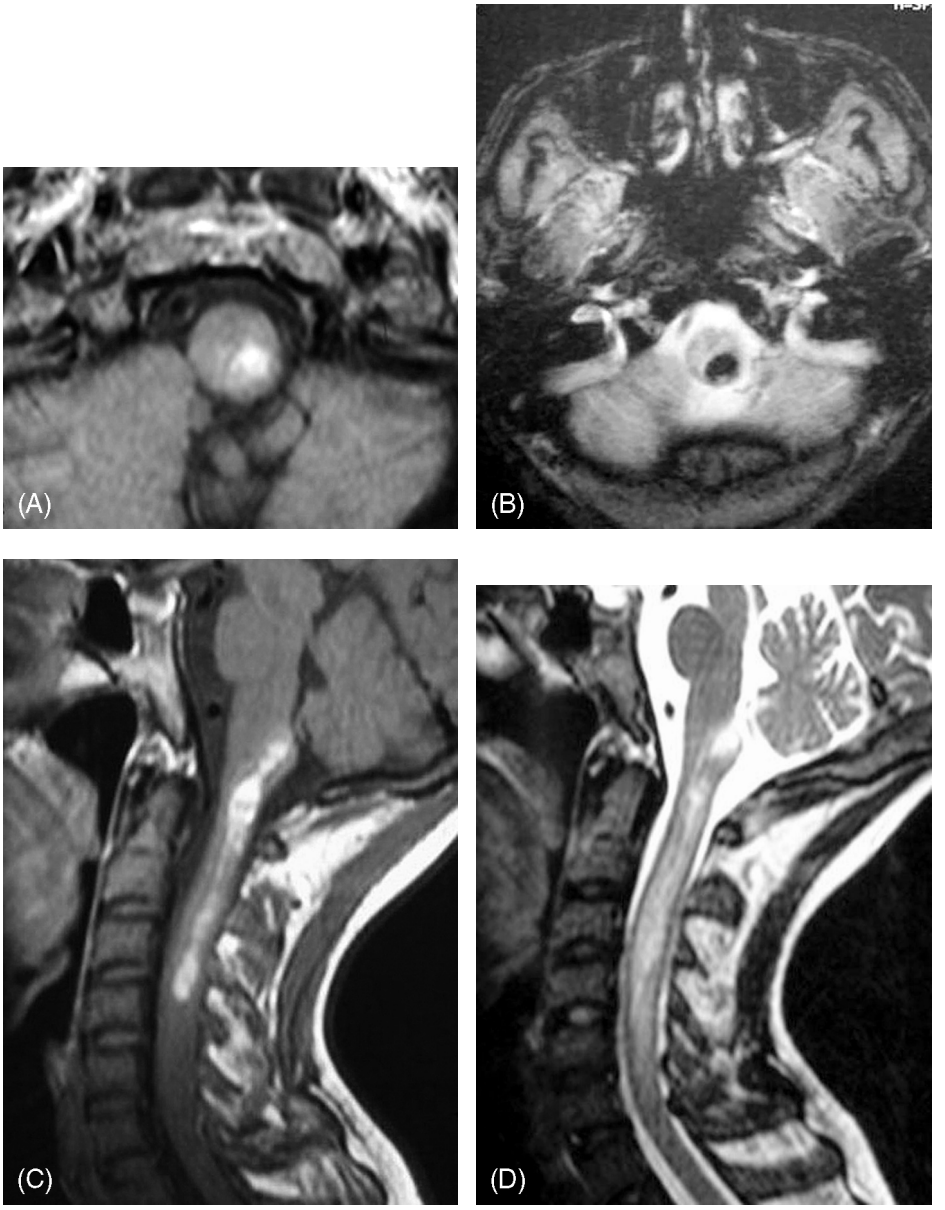

Fig. 34.4. Thirty-four-year old man with history of familial Mediterranean fever (FMF), secondary amyloidosis, and hemorrhagic diathesis. (A and B) Axial T1- and gradient T2-weighted images. (C and D) Sagittal plane T1- and T2-weighted images obtained in the first and second weeks after quadriparesis following acute onset of neck pain. Delayed images show better intensity difference and display the actual extension of the intramedullary hematoma.

(AVMs). They observed hematomyelia in 36% of cases with intradural AVMs presented with spinal hemorrhage. Intramedullary hemorrhage composed less than 1% of 604 patients with spinal hematoma (Kreppel et al., 2003). Rare causes of intramedullary hemorrhages have been reported in the literature. Allen et al. (1991) reported a case of medullary syndrome that developed without pain in a 15-year-old boy 6 years after irradiation for leptomeningeal spread of an intraventricular germinoma. In this patient intramedullary bleeding was detected with MRI and the hematoma was removed surgically. The authors argued that vasculopathy as a late complication of radiation therapy could be the cause of bleeding considering the fact that no tumor or other vascular anomaly was detected upon pathological examination.

34.3.2. Subarachnoid hemorrhage

Like other spinal hemorrhages, spinal subarachnoid hemorrhage usually presents with acute pain in the site of bleeding. Pain spreads rapidly along the spine and wraps up the body. In upper dorsal bleedings pain is felt between the scapulae. Opisthotonus may develop, and Kernig and Lasegue signs are usually positive. Radicular and medullary signs may develop depending on the severity of the bleeding. Sphincter abnormalities may develop. In cervical hemorrhages blood may rapidly enter the intracranial compartment, after which it might not be possible to differentiate spinal from intracranial subarachnoid hemorrhage. Altered consciousness and epileptic seizures may be observed. Intracranial hypertension may develop as an early or late complication of spinal subarachnoid hemorrhage. When blood collects at the lower end of the spinal canal, radicular pain becomes prominent. In these patients, performing a lumbar puncture would be difficult due to spinal rigidity.

Spinal subarachnoid hemorrhage may develop due to injury to the spine, cord, and the meninges. Spontaneous hemorrhage consists of less than 1% of nontraumatic spinal subarachnoid hemorrhages. The leading causes are intradural arteriovenous malformation and tumors (Wisoff, 1996). Neurinomas, menengiomas, and ependymomas are the tumors commonly causing spinal subarachnoid hemorrhages (Prieto and Cantu, 1967; Nassar and Correll, 1968; Heidrich, 1975). Kreppel et al. (2003) found that tumoral lesions accounted for 30% of spinal subarachnoid hemorrhages. The second most common cause was spinal vascular malformations. Data on spinal subarachnoid hemorrhages related to vascular malformations are based on case series in the literature. In their review of 60 spinal arteriovenous malformations, Aminoff and Logue (1974a) found a 10% incidence of subarachnoid hemorrhage. Houdart et al. (1966) reported that in 25% of all spinal vascular malformations the first symptom was subarachnoid hemorrhage and the rate of recurrent bleeding was 30%. In their review of 81 arteriovenous malformation cases from 1964 to 1985, Rosenblum et al. (1987) found that 33% of 54 intradural arteriovenous malformations presented with subarachnoid hemorrhage and that figure reached 52% over time. Berenstein et al. (2004) stated that 45% of their intradural arteriovenous malformation cases presented with spinal hemorrhage and that 64% of those were of the subarachnoid type. Spinal aneurysm and related subarachnoid hemorrhage is rare. In the literature subarachnoid hemorrhages associated with anterior spinal artery, posterior spinal artery, or radicular artery aneurysms have been reported (Garcia et al., 1979; Vincent, 1981). Furthermore, hemorrhages due to spinal pseudoaneurysm in systemic lupus erythematosus (Fody et al., 1980) and Behçet's disease (Bahar et al., 1993) have been reported.

34.3.3. Subdural hemorrhages

Spinal subdural hemorrhages are encountered much less often than epidural variants. Rupture of the bridging veins due to microtraumas is the major cause of intracranial subdural hematomas. Owing to anatomical differences, this mechanism would not work in the spinal canal (Generalli and Meaney, 1996). Example cases in the literature usually recommend thrombocytopenia or an attempt at a lumbar puncture for patients with hematological malignancies. One may encounter in the literature different reasons causing spinal subdural hemorrhage as isolated case reports. For instance, there are reports of spinal subdural hematoma after spontaneous resolution of cranial subdural hematoma (Bortolotti et al., 2004) or bleeding as a complication of cranial surgery (Lee and Hong, 2003). The treatment of choice is surgical evacuation. There is not much knowledge about the prognosis. However, Thiex et al. (2005) spoke of poor prognosis from their experiences with eight cases. They claimed that the prognosis depended on the preoperative neurological status.

34.3.4. Epidural hemorrhages

Spinal epidural hemorrhages are the most common type of spinal hemorrhages (Kreppel et al., 2003). Epidural hemorrhages are considered to be of venous origin (Wisoff, 1996). The epidural venous plexus rests in the fatty tissue in the spinal epidural space, where there are transverse connections between the anterior

and posterior epidural venous plexus at the level of the vertebral body (Groen et al., 1997, 2005).

Spinal epidural hemorrhages are twice as common in men as in women. In adults it is usually seen in the fifth to seventh decades (Kreppel et al., 2003). Etiologic causes include spinal or epidural anesthesia, iatrogenic coagulation defects or those associated with hematological disorders, straining, minor trauma, paravertebral vascular malformations increasing epidural venous pressure, vertebral hemangiomas, ankylosing spondylitis, and Paget's disease (Sawin et al., 1995; Wulf, 1996). Rare causes of epidural hemorrhages such as epidural hematoma resulting from rupture of a synovial cyst (Brown and Stambough, 2005) and epidural hemorrhage caused by extradural varix (Akutsu et al., 2003) have also been reported in the literature. Clinical findings are similar to other spinal hemorrhages. The main features are acute local pain and radicular signs. Signs of cauda equina compression may develop insidiously with lumbar epidural bleeding. In such cases, it might be clinically difficult to differentiate other processes causing compression in the lumbosacral region.

Developing MRI technology made it possible to diagnose spinal epidural hematomas more easily, raising debates on available treatment methods (Sklar et al., 1999; Duffill et al., 2000). With MRI, a diagnosis can be made readily with the detection of hyperintense blood signals in the epidural compartment in T1- and T2-weighted images. Differential diagnosis might be difficult in the first few days when the hematoma is isointense in T1-weighted images (Lovblad et al., 1997). In these cases, dural enhancement with intravenous gadolinium injection is helpful in localizing the lesion (Fukui et al., 1999; Chang et al., 2003). In their retrospective analysis of 20 cases with MRI, Chang et al. (2005) found that prognosis was poor in patients with severe neurological deficits and myelomalacia evident in T2-weighted images. The severity of the neurological deficits and the timing of surgical intervention are factors determining the prognosis (Foo and Rossier, 1981; Gelabert et al., 2003). Rohde et al. (2000) observed a better outcome in surgically treated patients with non-spontaneous epidural hemorrhages than those with spontaneous hemorrhages.

It is generally considered that early decompressive surgery is helpful in treating spinal epidural hematomas. The first successful surgical decompression for a spinal hematoma that was a traumatic epidural hemorrhage was performed by Jonas in 1911 (Mattle et al., 1987). A literature survey (Kreppel et al., 2003) revealed that the best results were obtained in those cases that were decompressed in the first 12 hours. Groen (2004) compared the results of 64 conservatively followed cases with 474 cases in the literature that were surgically treated. Comparisons highlighted the fact that the cases that did not undergo surgical intervention were patients who had milder neurological signs. The increase in the number of cases followed conservatively in the literature may be explained by early detection (with MRI) of mild cases.

34.4. Spinal vascular malformations

Indeed clinical knowledge about the circulatory anatomy of the spinal cord and its arteriovenous malformations dates back to late eighteenth century. Initial records about the vascular anatomy of the spinal cord include the contributions of Adamkiewicz in 1882. In one of his collections about intradural spinal arteriovenous malformations, Yasargil (1976) stated there were records belonging to Hebold (1885) and Gaupp (1888) about the entity. Despite cerebral angiography being first performed in 1927 by Egas Moniz, the clinical application of selective angiography of the spinal arteries was not performed until the 1960s.

Since this time, a growing number of papers released in the literature have initiated better understanding of lesion types, clinical features, and prognosis (Doppman et al., 1969; Aminoff and Logue, 1974a,b). This also led to categorization of the lesions mainly in the light of radiological findings and understanding the pathophysiological mechanisms leading to neurological symptoms. One of the most important contributions towards the understanding of spinal vascular malformations came with the definition of dural arteriovenous fistulas by Kendall and Logue (1977).

Spinal vascular malformations have been classified in different ways, most of which correspond to morphological details extracted from radiological findings. Spetzler et al. (2002) offered a new classification designed to allow more precise diagnosis and management. After describing spinal vascular lesions as neoplastic, arteriovenous fistulas (AVF), arteriovenous malformations (AVM), and aneurysms, they subdivided AVFs and AVMs according to their relationship to the dura; the AVFs as intradural and extradural variants, and the AVMs as intradural–extradural and intradural variants. The intradural arteriovenous malformation was then subclassified into intramedullary and intramedullary–extramedullary types. Rodesch et al. (2002) instead suggested that the arteriovenous shunts of the spinal cord do have specific biological attitudes determining their dynamic features, and it would not be correct to classify these lesions simply by regarding their morphological appearances. The authors also

defended the idea that understanding the genetic basis, the different embryological developmental stages, and the behavior of these biological involvements would play a role in clinical handling and management of patients. They claimed it would be possible to replace occlusive therapeutic methods by mending the actual defect with biological, medical, or genetic corrections. They reviewed 155 intradural arteriovenous shunts of the spinal cord and, according to the clinical and radiological findings, collected them under three major topics: genetic hereditary diseases, genetic nonhereditary diseases, and single lesions.

Despite the growing capability of imaging technology, the real incidence of spinal vascular malformations is not known. Among a total of 961 spinal mass lesions, Yasargil (1976) stated that 4.47% were vascular malformations. This ratio in brain tumors is similar, 4.42% of total lesions according to the author. Also, it has been stated that spine and spinal cord vascular malformations and their ratio to total of various spinal space occupying lesions ranged from 3% to 16% (Berenstein et al., 2004).

If we categorize arteriovenous lesions according to the shunt type, two features are apparent. If the connection is direct and a fistulous flow is present, then AVF is considered, or else the feeder and draining pedals appear to be centered around a nidus, and an AVM is considered. Fistulous connections may differ according to the amount of flow. Microfistulas or macroAVFs can be considered. It is possible to classify spinal vascular malformations according to their locations and their relation to spinal canal and spinal cord (Rodesch and Lasjaunias, 2003).

34.4.1. Paraspinal arteriovenous shunts

These are considered to have an embryological evolution of notochord origin (Berenstein et al., 2004). These shunts are fed by the segmental artery and tend to be present more in females at the thoracic level. Dilated venous structures may erode the nearby bone and directly compress the spinal cord. Reflux to the epidural space from venous elements may also cause neurological symptoms secondary to congestive myelopathy (Goyal et al., 1999). Subarachnoid and intraventricular bleeding has also been reported as a result of intracranial extension of draining veins, an outcome of draining vein rupture (Rodesch and Lasjaunias, 2003).

34.4.2. Extradural arteriovenous shunts

These develop in the epidural space. They are fed through the dural or epidural branches of the segmental artery of the affected level. Neurological symptoms appear when draining vessels go directly to the venous system of the spinal cord.

34.4.3. Dural arteriovenous shunts

These are the most common spinal vascular malformations in the elderly. They are five times more frequent in males and tend to occur after the fifth decade. Dural arteriovenous fistulas may be located in the thoracic, lumbar, or sacral regions. The general features and specific attributions to this class belong to definitions supplied by Kendall and Logue (1977) and Merland et al. (1980).

These arteriovenous shunts are intradural and are seen at the level of the intervertebral foramen. Fistulous connection in the dural shunt is generally fed from branches of the dorsal spinal artery. Increasing pressure in the venous side would reverse the venous flow, and the ultimate draining structures penetrate the dura to enter the perimedullary venous system, almost at the level of the relevant root sleeve. Dilated perimedullary venous structures are usually located in the posterior side of the spinal cord. These perimedullary draining veins usually tend to carry blood to a higher level, the thoracic or cervical region, or high up to the intracranial venous system. Progressive myelopathy is the major clinical outcome seen in 80% of cases. As the disease progresses, one might encounter both spinal and second motor neuron signs at the same time. Acute paraparesis or a relapsing and remitting pattern can occur. A few cases have been reported with symptomatology of subarachnoid hemorrhage secondary to cervical dural arteriovenous fistula (Do et al., 1999).

Spinal venous anatomy and pathophysiological mechanisms for dural AVFs have been evaluated in operated patients (Kendall and Logue, 1977; Tadie et al., 1985; McCutcheon et al., 1996). It has been accepted that a pathophysiological mechanism leading to spinal injury is increased venous pressure (Hurst et al., 1995). The idea was proposed by Aminoff et al. (1974), who investigated the AVMs and their clinical and prognostic features. Since the time of the definition of the spinal dural arteriovenous shunts, proximal closure of the main draining vein appeared to be a useful method of treatment (Logue et al., 1974; Logue, 1979; Oldfield et al., 1983; Symon et al., 1984; Rosenblum et al., 1987; Van Dijk et al., 2002).

34.4.4. Intradural arteriovenous shunts

These lesions may be found in the spinal cord, in the nerve root, or in the filum terminale. Spinal cord

arteriovenous shunts may be superficial or may be located deep in the tissue of the cord and be fed through the radicular–medullary or radiculopial arteries. The draining structures are the pial veins or the intrinsic venous system. It has been reported that some lesions may have venous drainage high up to the intracranial venous system. Spinal cord AVMs might be the fistulous type without having any convening nidus. Fistulous lesions of the spinal cord may be fed from the anterior or posterior spinal arteries according to their location in a respective manner (Heros et al., 1986; Gueguen et al., 1987). In general, vascular malformative lesions of the filum terminale are of the micro-AVF type. Spinal arteriovenous malformations harboring a nidus do have a single large venous draining system in spite of many or at least more than one arterial feeder (Berenstein et al., 2004). Arteriovenous malformations of the spinal cord may be concomitant with dysplastic aneurysms or vascular ectasia secondary to high flow. Thrombosis in the venous limb may lead to venous infarction, or increasing luminal pressure may cause vessel wall tear and result in hemorrhage (Caroscio et al., 1980).

T1- and T2-weighted conventional MRI can display vascular lesions as tubular structures showing signal alterations as a function of flow. Paraspinal lesions with large arteriovenous shunts and large draining veins, their compressive effect on the spinal cord, as well as the secondary changes on the spinal cord can be detected on a conventional MRI. Findings can be posterior perimedullary small tortuous vessels and, if present, pathological signal alterations in the spinal cord would suggest dural AVF. Gadolinium DTPA-enhanced T1-weighted studies would ease the visualization of the dilated venous structures. Although spinal angiography remains the gold standard in the evaluation of spinal vascular malformations, MRI is able to display small intramedullary vascular structures within the scope of a routine examination, or alternatively may suggest the possibility of such lesions because of hemorrhage, atrophy, and signal alterations due to myelopathy (Fig. 34.5). Improvements to enhanced MR angiography (MRA) in recent years using fast gradient techniques in a 3D manner have enabled the use of MRA in the demonstration of spinal vascular structures. Enhanced fast gradient MR angiography may help better demonstration of the nidus and the draining veins, though it would be very difficult to differentiate the feeder from a draining structure (Bowen et al., 2003). MRA has a role in follow-ups after therapeutic interventions (Lee et al., 1998; Mascalchi et al., 2001). Sensitivity studies of MRI and MRA in dural AVFs have revealed that contrast-enhanced 3D MR angiography does help to define the level of the abnormality rather than the fistula itself (Saraf-Lavi et al., 2002).

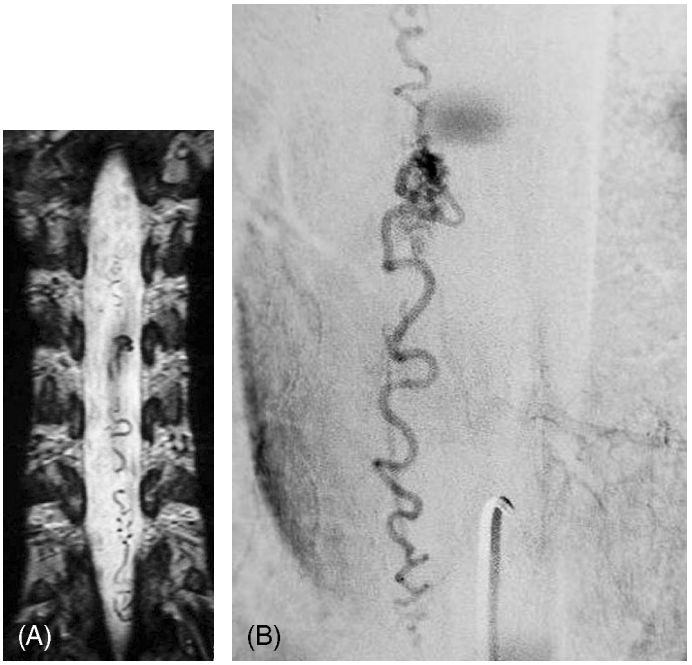

Fig. 34.5. MRI and DSA images of intramedullary AVM. (A) Coronal plane heavily weighted T2 image displaying the bright cerebrospinal fluid signal and serpentine hypointensive structures radiating down from the larger hypointensive nidus. (B) Digital subtraction angiography anterioposterior projection (DSA-AP) of the same patient with blushing nidus and large tortuous draining vein. Note the correlation of the images and the similarity of the draining pedal seen on either technique.

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Chapter 35

Extracranial and intracranial atheroma, and artery-to-artery embolism

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35.1. Introduction

Stroke remains the third leading cause of death and the commonest cause of disability in survivors. Worldwide, it affects 20 million people per year and results in 5 million deaths. Around 85% of strokes are ischemic in type. Effective secondary prevention treatment is available, but requires an understanding of the mechanism(s) of ischemia, as the pathogenesis is heterogeneous.

The major subtypes of ischemic stroke are large-artery atherosclerosis, cardiogenic embolism, small-vessel occlusion involving the deep perforating arteries, stroke due to rarer causes (e.g., arterial dissection, other arteriopathies, and procoagulant states), and a large group in which pathogenesis remains uncertain (Adams et al., 1993) (Table 35.1). Large-artery atherosclerosis is the most common subtype, accounting for around 50% of all ischemic strokes (Sandercock et al., 1989). The major complication of atherosclerosis is thrombosis, with local thrombotic occlusion or distal thrombo-embolism (Leys, 2001). Traditionally, this implied stenosis of the carotid arteries, but intracranial disease is accepted as more common than extracranial disease in some racial groups, and there has been recent recognition of the importance of the aortic arch as a source of artery-to-artery embolism. The following section will discuss the distribution of atheromatous disease, and the mechanisms of ischemia.

35.2. Distribution of atheroma

Atheroma affects large and medium-sized arteries, and has been divided into extracranial or intracranial vessel involvement. It occurs at certain sites, usually at sites of branching or tortuosity, rather than diffusely through the vessel. Although patients with atheroma at one site are likely to have atheroma elsewhere, there are distinct variations in the distribution of disease.

35.2.1. Carotid bifurcation atheroma

35.2.1.1. Historical considerations

The importance of carotid bifurcation disease was discovered early and consistently. Wepfer is credited with being the first to recognize the significance of carotid occlusion in 1658 and its relationship to underlying "fibrous masses" (atherosclerosis) and thrombus (Gurdjian, 1979). Willis (1664) related carotid occlusion to the risk of apoplexy. In the nineteenth century, Virchow and others related carotid occlusive disease to cerebral ischemic symptoms (Gurdjian, 1979). Chiari (1905) described thrombo-embolism from carotid atherosclerosis to intracranial vessels. In 1914, Hunt urged pathological examination of the major extracranial arteries in ischemic stroke—frequently overlooked in previous clinical and pathological studies. The importance of carotid occlusion was again highlighted by the introduction of arteriography by Moniz et al. in the late 1930s (Moniz et al., 1937). Despite these earlier publications, there was still a prevailing view in the early 1950s that most ischemic strokes were due to intracerebral artery thrombosis.

The work of Fisher in the early 1950s (Fisher, 1951) and a number of autopsy studies (Adams and Vander Eecken, 1953; Fisher, 1954; Hutchinson and Yates, 1957; Baker and Iannone, 1959; Martin et al., 1960; Schwartz and Mitchell, 1961; L'Hermitte et al., 1968; Blackwood et al., 1969; Castaigne et al., 1970; Torvik et al., 1989) changed this perception,

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Table 35.1

Pathogenetic subtypes of ischemic stroke. Modified from Adams et al. (1993)

Subtypes	Comments
1. Large-artery atherosclerosis	• The most common subtype worldwide • Usually due to thrombo-embolism • Typically extracranial in Caucasians; often intracranial in African-Americans and Asians
2. Cardio-embolism	• Most commonly due to nonvalvular atrial fibrillation • Uncertain management for rarer causes (e.g., patent foramen ovale)
3. Small-vessel occlusion	• A common stroke subtype, particularly in Asians • Usually due to in situ thrombosis, but may be embolic
4. Stroke of other determined etiology	• More prevalent in young adult stroke patients • Includes rarer causes, such as dissection, prothrombotic states, and vasculitis
5. Stroke of undermined etiology	• Despite adequate investigation, 20% of strokes remain cryptogenic

demonstrating that the predominant site for atherosclerosis was the extracranial internal carotid artery at the carotid bifurcation (Fig. 35.1). Intracranial lesions were found to be very rare. Fisher (1954) reported a 9.5% incidence of near or total occlusion of at least one extracranial carotid artery in 432 consecutive adult autopsies. At the same time, it was also demonstrated that the degree of atherosclerosis increased with age and could be asymptomatic (Whisnant et al., 1961).

Other studies in the late 1950s and early 1960s helped to reinforce Fisher's findings. Hutchinson and Yates (1957) showed that extracranial atherosclerosis was the major cause of cerebral infarction; while Martin et al. (1960) confirmed that the maximal degree of carotid atherosclerosis was present at the carotid bifurcation and in the proximal 2 cm of the internal carotid artery. Whisnant et al. (1961) showed that most patients with cerebral ischemia had greater

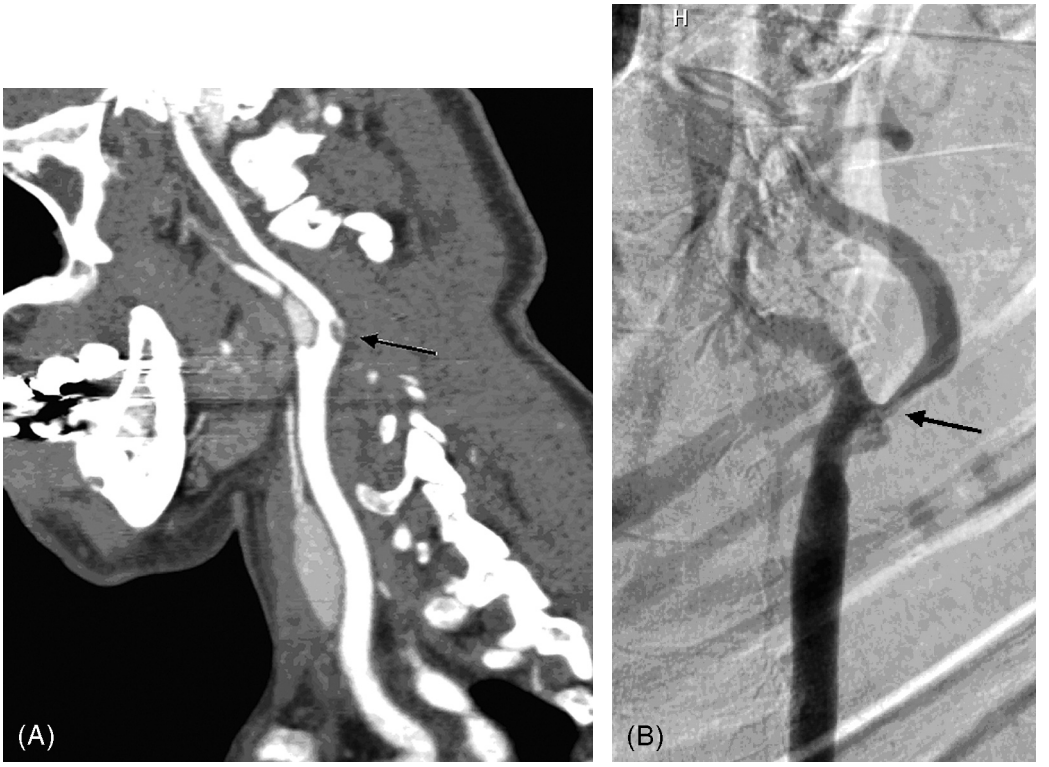

Fig. 35.1. Carotid bifurcation atheroma on CT angiography (A) and digital subtraction angiography (B). Images courtesy of Dr. Bernard Yan, Department of Neurology, Royal Melbourne Hospital.

than 50% stenosis of at least one major extracranial artery. Blackwood et al. (1969) found a good correlation between atheromatous internal carotid obstruction and intracranial occlusion, and that in situ middle cerebral artery thrombosis was, in fact, very uncommon. Lhermitte et al. (1968) and Castaigne et al. (1973), studying patients with cerebral ischemia, found that atherosclerotic internal carotid artery occlusion with superimposed thrombosis was common. Recent and old emboli in the intracranial distribution and anterograde thrombus from the site of the occlusive thrombosis into the brain were frequent findings. These, and more recent autopsy studies (Lammie et al., 1999), indicated that the thrombus often found at autopsy in intracranial vessels emanated from extracranial atherosclerotic lesions.

35.2.1.2. Ultrasound studies

The location of the internal carotid artery in the neck makes it highly accessible to non-invasive examination. Carotid ultrasound studies confirmed the findings of autopsy studies in larger cohorts. Colgan et al. (1988) found that only 4% of 348 unselected volunteers had greater than 50% carotid stenosis. Josse et al. (1987) found that in men aged 75–84 years, 6.1% had greater than 50% stenosis. Prati et al. (1992) found a 25% prevalence of carotid atherosclerosis, both intimal–medial thickening and frank plaque formation. Hennerici et al. (1981) studied 2,009 asymptomatic patients with severe peripheral or coronary heart disease or with multiple risk factors. They found a particularly high correlation between carotid disease and peripheral atherosclerosis. Li et al. (1994) insonated the extracranial carotid arteries in 14,046 individuals in a community-based study and showed correlations between plaque development, age, Caucasian race, and male gender.

35.2.1.3. Gender differences

Several population studies have shown that carotid atheroma is more prevalent in men (Prati et al., 1992; Li et al., 1994). It is well recognized that women have fewer cardiovascular events than men, which has been attributed in part to the protective effects of estrogen on the endothelium and differences in risk factor profiles (Weidner, 2000; Iemolo et al., 2004). However, recent studies have examined sex differences in carotid bifurcation anatomy and plaque distribution. Schulz and Rothwell (Schulz and Rothwell, 2001) analyzed the carotid angiograms of patients randomized into the European Carotid Surgery Trial, and showed that women were more likely to develop disease of the external carotid artery whilst men were more likely to have maximum stenosis distal to the bulb of the internal carotid artery. Additionally, the anatomy of the carotid bifurcation differed between men and women. Women had a larger internal carotid artery and smaller external carotid artery, relative to the common carotid artery, than men, and this may result in different flow patterns, which in turn influence the development and distribution of plaque (Schulz and Rothwell, 2001). Iemolo et al. (2004), using high-resolution duplex scanning, confirmed that women were less likely to have plaque than men, yet had greater stenosis. Only plaque area predicted outcome, and the authors hypothesized that the greater stenoses observed in women was a technical issue related to higher velocities in smaller arteries.

35.2.1.4. Concurrent cerebral atherosclerosis and coronary artery disease

The finding of carotid atheroma, at least in Caucasian populations, strongly predicts the finding of atheroma elsewhere. Fisher et al. (1965) emphasized the association between extracranial cerebrovascular disease and coronary artery disease in a large autopsy study. Myocardial infarction was much more common in patients with stenosis or occlusion of cervical carotid arteries. Many other studies have confirmed this relationship, including a link between coronary atherosclerosis and silent cerebral infarction. One study (Nishino et al., 1993) also showed a correlation between progression of coronary and carotid atherosclerosis on ultrasound.

Tanaka et al. (1993) evaluated both coronary and cerebrovascular atherosclerosis in patients with ischemic heart disease. They found that patients with silent cerebral infarctions were older and had a greater extent of coronary atherosclerosis. There is also a strong association between transient ischemic attacks (TIAs) and coronary artery disease (Scheinberg, 1991). Salonen and Salonen (1993) studied intimal–medial thickness with B-mode ultrasound and found that for each 0.1 mm of common carotid intimal–medial thickness, the risk of myocardial infarction increased by 11%.

35.2.2. Vertebrobasilar atherosclerosis

The two vertebral arteries arise from the subclavian arteries and ascend protected in the cervical spine. Vertebral disease is thus more difficult to document by non-invasive means than carotid disease. There are also frequent anatomic variations (often one very small vertebral artery or a vertebral artery that terminates in the internal carotid artery) that can influence clinical symptoms. Thus less is known about the prevalence and natural history of vertebrobasilar disease.

In Hutchinson and Yates' (1956, 1957) pathological studies of 48 patients, proximal vertebral atherosclerosis was present in 19 stroke patients, contrasting with the less affected intracerebral arteries. Caplan et al. (1992) presented a series of 10 patients with posterior circulation infarcts who had been studied with catheter angiography. All had severe atherosclerosis at the origin of the vertebral arteries. This led the authors to conclude that extracranial vertebral artery disease was a similar process to internal carotid artery atheroma, at least in Caucasian patients.

In contrast, Fisher et al. (1965) found that all symptomatic vertebrobasilar occlusions were intracranial, and that cervical occlusions tended to be asymptomatic. Various authors (e.g., Schwartz and Mitchell, 1961) found that vertebral atherosclerosis was less common and severe than carotid disease. Castaigne et al. (1973) found that the distal vertebral artery was more commonly affected by thrombosis than the proximal vessel, while nearly all basilar artery occlusions were due to localized atherosclerosis, rather than embolism from a proximal source (Fig. 35.2).

35.2.3. Intracranial atherosclerosis

In the 1950s, Adams and Vander Eecken (1953) observed that the common sites for atherosclerosis were the carotid bifurcation, carotid siphon, the middle cerebral stem, the second segment of the anterior cerebral artery, and the vertebrobasilar system. Subsequent studies suggested that intracranial disease was much less common than extracranial disease, and was said to be responsible for only 5–10% of ischemic strokes. However, Caplan (1986) pointed out that most autopsy and angiographic studies had been performed on white, predominantly male subjects and were thus biased.

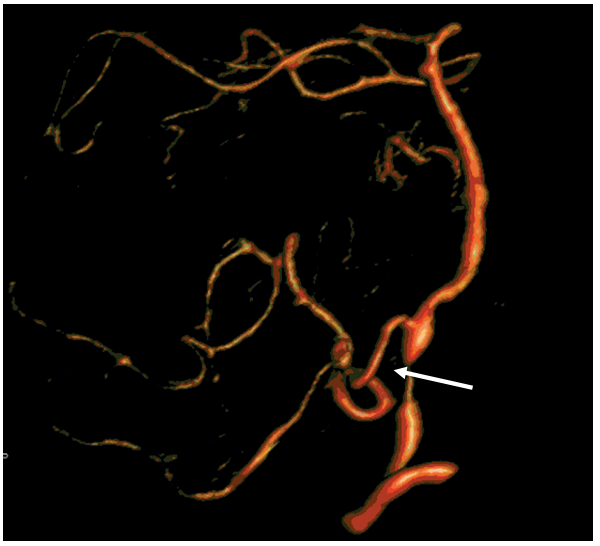

Fig. 35.2. Distal vertebral artery atherosclerosis on CT angiography. Image courtesy of Dr. Bernard Yan, Department of Neurology, Royal Melbourne Hospital.

35.2.3.1. Racial differences

Caplan demonstrated that intracranial atherosclerosis was more common in black, Asian, female, and diabetic patients (Caplan et al., 1985, 1986; Caplan, 1989) (Fig. 35.3 and Table 35.2). These findings have been confirmed by many subsequent studies. The Joint Study of Extracranial Arterial Occlusion (Heyman et al., 1972) reported more occlusive, intracranial disease in black patients. Other investigators (Gorelick et al., 1984; McGarry et al., 1985; Caplan et al., 1986; Ryu et al., 1989; Gil-Peralta et al., 1990) also showed that African-American patients had more atherosclerotic lesions of the supraclinoid internal carotid artery and the middle cerebral artery stem, contrasting with the extracranial predominance in white patients, and that these differences could not be explained by variations in risk factors. Caplan's group (Gorelick et al., 1985; Caplan et al., 1986) found that while white patients had more lesions of the vertebral origins, black patients had more lesions in the distal basilar and intracranial posterior circulation vessels.

Sacco and colleagues (Sacco et al., 1995) demonstrated that intracranial atherosclerosis was more frequent in Hispanic as well as black patients. The unadjusted odds ratio for nonwhites (blacks and Hispanics combined) was 0.8 (confidence interval (CI: 0.4–1.8) for extracranial and 7.8 (CI: 1.04–57.7) for intracranial atherosclerosis. Patients with intracranial disease were significantly younger and had an increased frequency of hypercholesterolemia and insulin-dependent diabetes compared with those with nonatherosclerotic disease. In part this was due to differences in risk factor profile, but the odds ratio for intracranial atheroma was still 4.4 (CI: 0.6–35) after controlling for age, education, insulin-dependent diabetes, and hypercholesterolemia.

The pattern of predominant intracranial atherosclerosis in African-Americans appears to be similar to findings in Asian populations, both exhibiting intracranial lesions in the large arteries, as well as a greater rate of small-vessel disease and lacunar infarction (Mitsuyama et al., 1979; Leung et al., 1993; Reed et al., 1994; Wong and Li, 2003; Moussouttas et al., 2006). Evidence is emerging that the long-term mortality and stroke risk of intracranial atheroma is at least as bad as high-grade extracranial atherosclerotic lesions (Wong and Li, 2003; Weimar et al., 2006).

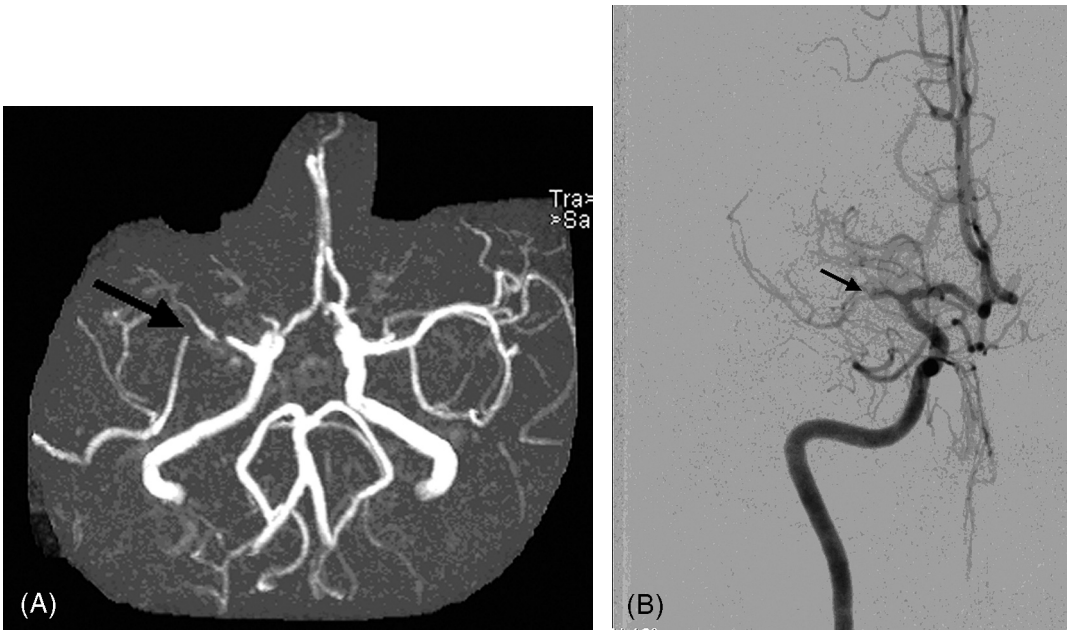

Fig. 35.3. Middle cerebral artery atherosclerotic stenosis on magnetic resonance angiography (A) and on digital subtraction angiography (B). Images courtesy of Dr. Bernard Yan, Department of Neurology, Royal Melbourne Hospital.

Table 35.2

Racial differences in cerebrovascular atherosclerosis

Population group	Distribution of atherosclerosis
Caucasians	• Predominantly extracranial disease • Common carotid bifurcation • Vertebral artery origins and distal sites • Basilar artery • Aortic arch
African-Americans	• Predominantly intracranial disease • Supraclinoid internal carotid artery, middle cerebral stem • Distal basilar, intracranial posterior circulation
Asians	• Predominantly distal intracranial atherosclerosis • Middle cerebral stenosis and lacunes common

35.2.4. Aortic arch atheroma

The aortic arch is a prominent site for the formation of atherosclerosis (Martin et al., 1960; Fisher et al., 1965). It is seen in early adult life, and its incidence and severity increases with age (Macleod et al., 2004). Early population-based autopsy studies showed that the prevalence of aortic arch atheroma reached 33% in those aged 55–64 years (Strong et al., 1978). Using an autopsy databank, Amarenco et al. (1992) found that complex aortic arch plaques occurred in 28% of patients with cerebral infarction. However, it was unclear whether arch atheroma reflected simply a generalized tendency to vascular disease, or was the actual source of embolus resulting in the stroke.

The diagnosis of arch atheroma in life generally requires transesophageal echocardiography (TEE), which had not been widely used in stroke patients until the 1990s. The importance of arch atheroma in the pathogenesis of cerebral ischemia was then recognized as an independent risk factor for ischemic stroke, presumably as an embolic nidus (Tunick et al., 1991). Davila-Roman et al. (1994) used intraoperative aortic ultrasound on 12,000 patients undergoing cardiac

surgery, finding aortic arch atheroma in 19.3% of patients, independently correlating with a history of cerebral ischemia, age, smoking, or coronary or peripheral vascular disease. In a prospective case-control study using TEE (Amarenco et al., 1994), atherosclerotic plaques of thickness greater than 4 mm were found in 14.4% of patients with ischemic stroke, but in only 2% of controls, such plaques being most common in patients without a known cause of stroke (Fig. 35.4). The hazard ratio for stroke increased with plaque thickness, from 3.3 (CI: 1.7–6.5) for atheroma of 1–2 mm thickness to 13.8 (CI: 5.2–36.1) for atheroma of 4 mm or greater. Similarly, Jones et al. (1995) found that aortic arch atheroma was an independent risk factor, with increased odds of 7.1 for complex atheroma.

A recent study suggested that both thickness and extent of aortic atheroma predicted recurrence of ischemic stroke (Fujimoto et al., 2004). McLeod et al. (2004) reviewed several studies with acceptable follow-up data, and found that the odds ratio for recurrent stroke in the presence of severe (4 mm or greater) arch atheroma was 3.76 (CI: 2.57–5.51). This analysis included a subset of patients from the Stroke Prevention in Atrial Fibrillation III study who underwent TEE (Stroke Prevention In Atrial Fibrillation Investigators Committee On Echocardiography, 1998). Those with severe arch atheroma (134 of 382 patients) experienced a 10% stroke rate over 1 year of follow-up, compared with 4% in those with no or moderate atheroma. Optimal secondary prevention in patients with severe aortic arch atheroma remains unknown. The Aortic Arch Related Cerebral Hazard (ARCH) study is comparing the efficacy and safety of a combination of clopidogrel and aspirin with warfarin, in prevention of stroke and other vascular endpoints (Macleod et al., 2004).

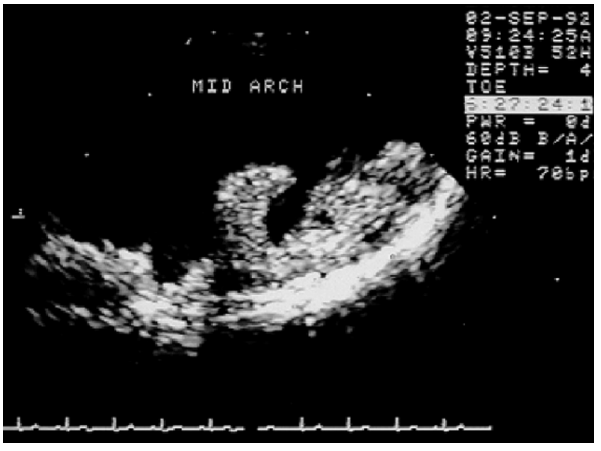

Fig. 35.4. Arch atheroma on TEE.

35.3. Mechanisms of ischemia

The precise mechanisms of cerebral ischemia were historically difficult to study. In the mid-nineteenth century, Virchow noted that gangrene was sometimes caused by clots originating in the heart (a process he called embolism), and extrapolated these observations to stroke. However, for many years sources of embolism other than the heart were rarely considered as causes of infarction. Stroke not due to cardiac embolism was thought to be due to thrombosis of intracranial vessels. Until the mid-twentieth century, a popular notion was that transient ischemic attack (TIA) was due to local vessel spasm, but this was discredited with the widespread use of catheter angiography in the mid-1950s.

Early workers emphasized the importance of hemodynamic mechanisms in transient or sustained cerebral ischemia. For instance, Denny-Brown (1951, 1960) considered that internal carotid stenosis could produce a state of "episodic insufficiency" in the circle of Willis, whereby a hemodynamic crisis could be produced by systemic hypotension. Meyer et al. (1956) also described "cerebral hemodynamic crises." This theory helped to popularize carotid endarterectomy, a procedure widely (and often inappropriately) performed until randomized controlled trials defined its place.

Pickering (1948) first proposed an embolic basis for TIAs. He suggested that they were due to transient obstruction of a cerebral artery or arteriole. Fisher (1951, 1954) coined the term "transient attacks" and linked them to extracranial occlusive disease. He later reported the efficacy of anticoagulants in their prevention, favoring embolism as a cause rather than a hemodynamic mechanism (Fisher, 1958). Detailed observations of the retinal circulation by Fisher (1959) and Russell (1961), recording microemboli during amaurosis fugax, supported the embolic hypothesis. Gunning et al. (1964) reported a series of TIAs and ischemic strokes associated with ipsilateral mural thrombus in the extracranial carotid artery. However, Fisher (1976) and Duncan et al. (1976) claimed that hemodynamic factors were a more likely explanation than microemboli in those patients with frequent, brief, stereotyped, transient ischemic attacks.

35.4. Artery-to-artery embolism

35.4.1. Large-artery disease, atherothrombosis, and thrombo-embolism

Large-artery atherothrombosis with thrombo-embolism is considered to be the major pathological determinant of ischemic stroke secondary to extracranial and intracranial atherosclerosis (Castaigne et al., 1970; Leys,

2001). The concept is that atheroma of a large vessel progressively deteriorates due to a combination of plaque growth and mural thrombus formation overlying the plaque. Eventually the mural thrombus embolizes, occluding a distal (usually intracranial) smaller vessel. Emboli typically travel via their normal arterial distribution to the retinal or brain blood vessels. Hence, the underlying pathology in most strokes is arterial thrombosis, involving a combination of platelet adhesion, activation, and aggregation, and is therefore similar to that in acute myocardial infarction.

Atherosclerosis is most strongly associated with hypertension, cigarette smoking, hypercholesterolemia, diabetes, and male sex. It is likely that these factors are causal. The strongest risk for ischemic stroke is increasing age, with most community-based studies reporting a median age of 75 in stroke patients. In the elderly, atherosclerosis is common, and ischemic stroke is most commonly due to the consequences of atherosclerosis (Sandercock et al., 1989). Even in young adults, where atherosclerosis is less common, it still accounts for between 15% (Marini et al., 1999) and 30% (Lanzino et al., 1991; Naess et al., 2005) of ischemic strokes in adults younger than 50 years.

Van Damme et al. (1992) histologically examined a series of carotid plaques, showing combinations of intraplaque hemorrhage, ulceration, and fresh and recanalized thrombus. The presence of fresh thrombus was the only significant clinicopathological correlation in symptomatic carotid disease. Fisher et al. (1987) found that patients with intraluminal thrombosis at endarterectomy had arteriographic evidence of severe carotid stenosis. Torvik et al. (1989) found that severe atherosclerotic stenosis was frequent, but not a prerequisite for thrombus formation, since occluding thrombi in carotid vessels could be seen without hemodynamic stenosis. Ogata et al. (1990) suggested that the mechanism of carotid occlusion producing stroke was a rupture of the fibrous lining of the arterial wall over the nidus of bifurcation atheroma, producing tight luminal stenosis and thrombosis.

The detection of angiographic thrombus in ischemic stroke is likely to be related to the timing of the study. Hence, Buchan et al. (1988) noted that angiographic evidence of intraluminal carotid thrombus was rare, being identified in only 1.5% of angiograms performed for ischemic symptoms over 10 years, and generally associated with severe plaques. In contrast, Bladin (1964) demonstrated a high frequency of both carotid occlusion and distal embolism on acute angiography of stroke patients. Fieschi et al. (1989) also found that a high proportion of ischemic stroke patients had intracranial vascular occlusions on acute angiography, performed within 6 hours of stroke onset. These could be attributed to thrombo-embolism, since most arteries subsequently recanalized. A significant minority of patients had ipsilateral internal carotid occlusions.

Occasionally, emboli may travel in collateral vessels when an artery is occluded. In patients with carotid occlusion and subsequent stroke, Barnett et al. (1978) described thrombo-embolism originating from the stump site. Either cerebral or retinal ischemia could be produced by the embolus traveling via the collateral anastamotic circulation between the external carotid artery and intracranial branches. The authors postulated that stump turbulence could produce progressive localized atherosclerosis and aggravated thrombogenesis, with delayed embolization.

35.4.2. Atheromatous embolism

The frequent finding of ulceration in carotid plaques at endarterectomy, and the observation of cholesterol emboli in the retinal vessels of some patients with amaurosis fugax, have supported the mechanism of artery-to-artery embolism in cerebral ischemia. However, atheromatous or cholesterol embolism has been less frequently documented than platelet–fibrin thrombo-embolism. Beal et al. (1981) reported the autopsy of a patient who died after multiple TIAs, in which many small cerebral arteries were occluded by cholesterol emboli, producing multiple small infarcts in both hemispheres. Masuda et al. (1994) reported 15 autopsy cases of cerebral atheromatous embolism. The emboli were composed mostly of cholesterol crystals, occluding arteries from 50–300 μm in diameter, producing borderzone infarcts or arterial territorial infarcts if the emboli were larger due to fibrin association.

Microembolic signals detected by transcranial Doppler ultrasound have received much attention recently. These high intensity signals reflect aggregates of platelets or cholesterol-rich atheroma (i.e., emboli) traveling in the vessel. Microembolic signals are associated with a variety of stroke subtypes, particularly large artery atherosclerosis and cardiogenic embolism. Their detection could be helpful in determination of stroke pathogenesis (Lund et al., 2000). They are most prevalent shortly after TIA and acute stroke, and also appear to be a marker of risk related to disease activity (Imray and Tiivas, 2005). The number of microembolic signals may be modified by antiplatelet therapy (Infeld et al., 1996; Imray and Tiivas, 2005; Markus et al., 2005).

There have been many clinical studies of microembolic signals in carotid disease (Imray and Tiivas,

2005) showing that they correlate with degree of stenosis, plaque morphology, and presence of ulceration. These studies support artery-to-artery embolism as a common mechanism of ischemia. Evidence to support the role of arch atheroma as a source of thromboembolism also comes from transcranial Doppler ultrasound studies. Microembolic signals were much more common in stroke patients with severe arch atheroma than in those without atheroma (Macleod et al., 2004).

35.4.3. Does plaque morphology and progression relate to atherothrombosis?

Based on the pathological examination of carotid plaques obtained at endarterectomy, and abnormalities in vessel imaging using angiography and Doppler ultrasound, differing manifestations of atherosclerosis have been linked to the development of ischemic symptoms. These include vessel stenosis, wall thickness, ulceration, and intraplaque hemorrhage. In addition, dynamic changes in atherosclerotic plaques, notably progression, have been correlated with the development of ischemic symptoms (Touboul, 1994).

Of the various parameters of cerebrovascular atherosclerosis, the degree of plaque stenosis bears the clearest relationship with ischemic symptoms. In NASCET (North American Symptomatic Carotid Endarterectomy Trial Collaborators, 1991), the risk reduction ranged from 12% for ipsilateral stroke at 2 years in those with 70–79% stenosis, up to 26% for 90–99% stenosis. The European Carotid Surgery Trial (European Carotid Surgery Trialists' Collaborative Group, 1991) showed that patients with mild carotid stenosis (< 30%) were at very low risk for cerebral ischemia.

Fisher and Ojemann (1986) serially sectioned carotid endarterectomy plaques, and found that neurological deficits correlated best with carotid occlusion or severe stenosis. Similarly, studies of the natural history of asymptomatic carotid disease have shown a strong correlation between the degree of stenosis and the risk of stroke, particularly with high-grade stenosis (Johnson et al., 1985; Bogousslavsky et al., 1986; Chambers and Norris, 1986; O'Holleran et al., 1987).

Carotid plaque ulceration has long been cited as an important factor in the development of artery-to-artery embolism (Bartynski et al., 1981; Imparato et al., 1983; Zukowski et al., 1984; Gomez, 1990; Perez-Burkhardt et al., 1994; Rothwell et al., 2000) (Fig. 35.5). Other authors, however, have questioned the relevance of plaque ulceration in the causation of ischemic symptoms, pointing out that ulceration is usually associated with major stenosis (Wechsler, 1988). In NASCET

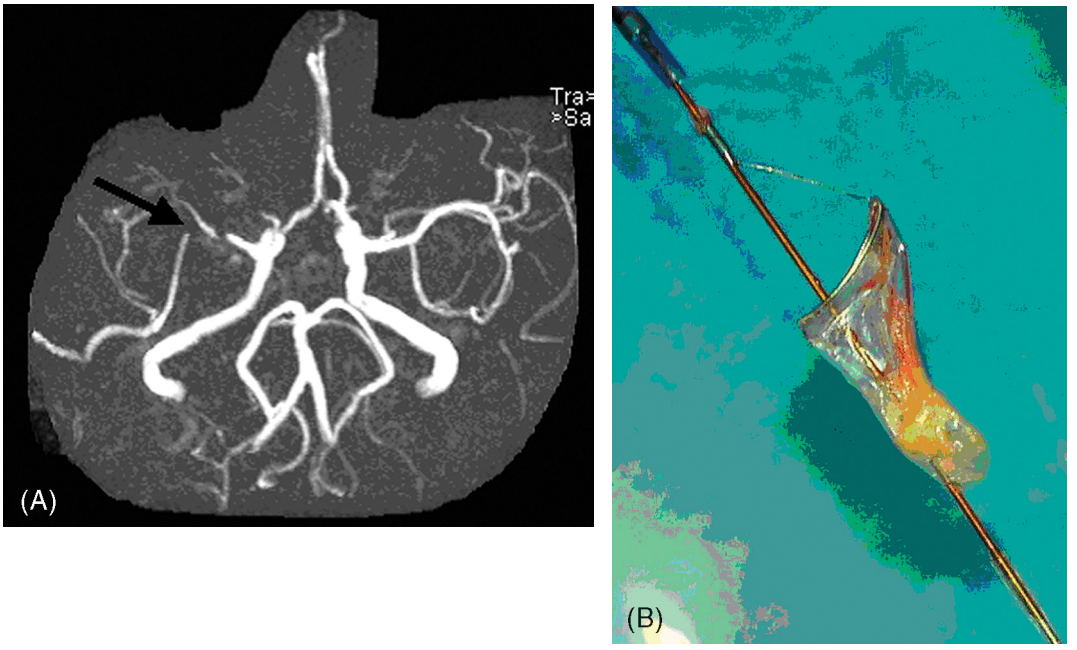

Fig. 35.5. Extensive carotid plaque on digital subtraction angiography (A) and plaque removed during endovascular intervention (B). Images courtesy of Dr. Bernard Yan, Department of Neurology, Royal Melbourne Hospital.

(Eliasziw et al., 1994) and ECST (European Carotid Surgery Trialists' Collaborative Group, 1991) the presence of ulceration substantially increased the risk of stroke for all degrees of stenosis.

Intraplaque hemorrhages are common in patients with stenotic atherosclerotic plaques, but their relationship to the development of cerebral ischemic symptoms is controversial, with conflicting reports from a large number of studies. Some studies concluded that intramural hemorrhage was important (Imparato et al., 1979; Lusby et al., 1982; Persson et al., 1983; Ammar et al., 1986; Fisher et al., 1987; Langsfeld et al., 1989) and correlated with ischemic symptoms. In contrast, others found no correlation between intraplaque hemorrhage and cerebral ischemia (Lennihan et al., 1987; von Maravic et al., 1991).

Changes in plaque size over time have been investigated using serial Doppler examinations and also in follow-up studies after either carotid endarterectomy or angioplasty. Progression has been correlated with the development of cerebral ischemic symptoms (Chambers and Norris, 1986; Bornstein and Norris, 1989).

35.4.4. Hemodynamic mechanisms

Despite early popularity for the hemodynamic theory, it is now recognized that the vast majority of ischemic strokes and TIAs are caused by occlusion of an intracranial artery by embolus or in situ thrombosis. Severe arterial stenosis/occlusion or good evidence of a fall in systemic blood pressure before onset are not observed in most ischemic strokes (Bladin and Chambers, 1994). However, it is possible that low flow could result in transient or fixed ischemia in certain clinical circumstances. These include onset of symptoms on standing up, immediately after a large meal, in hot weather or after a hot bath, after exercise, or during an operation if there is hypotension. Over-aggressive control of blood pressure resulting in hypotension is probably the most common clinical situation encountered.

35.4.4.1. Hemodynamic effects of carotid stenosis

In normal circumstances, large falls in blood pressure are well tolerated because of cerebral autoregulation (or if not tolerated, syncope is much more likely than focal symptoms). If a vessel is severely constricted, autoregulation may not be able to compensate and blood flow will fall in that area. This is particularly likely if the collateral circulation is compromised.

The hemodynamic effects of carotid stenosis have been well studied (Crawford et al., 1962; Brice et al., 1964; Deweese et al., 1970; Grady, 1984). Brice et al. (1964) found that a stenosis would reduce arterial blood flow if the cross-sectional area was less than 2 mm^2, but the effect of stenosis also depended on configuration, length and the number in series. Deweese et al. (1970) found that a residual lumen of less than 1 mm in diameter (approximately 63% diameter restriction) always produced a hemodynamic change, while a residual lumen of greater than 3 mm (47% narrowing) was never significant. Spencer and Reid (1979), using Doppler techniques, found that carotid flow would not be reduced until the luminal diameter was less than 1.5 mm.

Many workers reported impaired cerebral hemodynamics that improved following carotid endarterectomy, supporting a significant hemodynamic role in cerebral ischemia (Engell et al., 1972; Jones et al., 1972; Obrist et al., 1975; Takagi et al., 1979). Similar benefits were reported following extracranial–intracranial bypass surgery (Baron et al., 1981; Halsey et al., 1982; Meyer et al., 1982), but the hemodynamic hypothesis of cerebral ischemia received a severe setback when extracranial–intracranial bypass anastomosis was shown to produce no improvement over medical therapy (EC/IC Bypass Study Group, 1985). One study (Powers et al., 1989) found that patients with ischemic symptoms and abnormal cerebral hemodynamics on positron emission tomography (PET) did not necessarily have an increased stroke risk at follow-up.

35.4.4.2. Hemodynamic strokes—borderzone infarction

Although most nonlacunar cerebral infarcts are considered to have a thrombo-embolic pathogenesis, hemodynamic strokes involving external or internal borderzones (watershed regions) have now been well documented (Fig. 35.6). Hemodynamic infarcts can occur due to systemic hypotension, severe extracranial vascular disease, or a combination of these determinants (Bogousslavsky and Regli, 1986; Bladin and Chambers, 1994). Because of the topographic variability of the major cerebral arteries (van der Zwan and Hillen, 1991; van der Zwan et al., 1993), precise diagnosis of the arterial borderzones on computed tomography (CT) or magnetic resonance imaging (MRI) scans can be difficult. This variability in territorial volumes is related to normal differences in the arterial diameters of the anterior, middle, and posterior cerebral arteries (van der Zwan et al., 1993). The location of the borderzones may also be affected by the development of occlusive cerebrovascular disease (van der Zwan et al., 1993).

Bilateral watershed infarcts are not uncommonly seen following cardiac surgery. Studies suggest that around half are due to hypoperfusion (Rankin et al.,

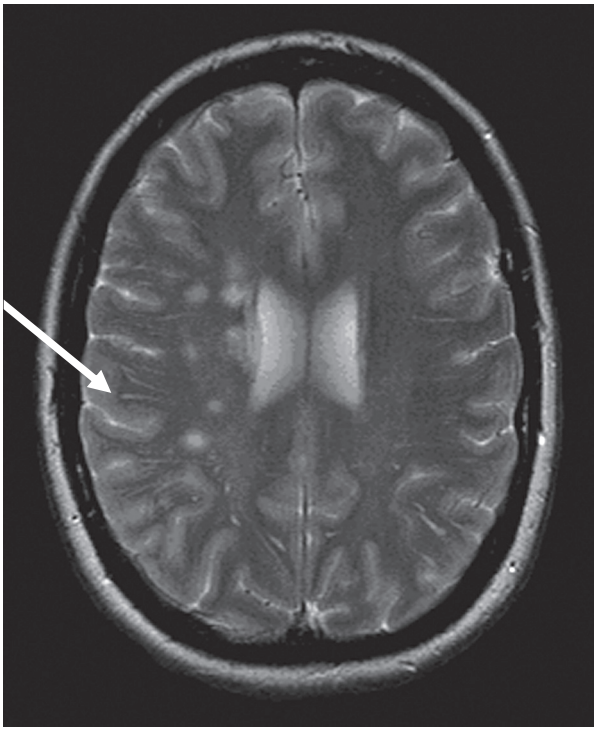

Fig. 35.6. Right hemisphere borderzone infarcts seen on T2-weighted axial MR image. Image courtesy of Dr. Bernard Yan, Department of Neurology, Royal Melbourne Hospital.

1994; Barbut et al., 1998). Typically, infarcts were multiple and involved the posterior watershed regions. Clinical features of bilateral posterior borderzone infarcts include cortical blindness, visual disorientation and agnosia, and amnesia. When unilateral, posterior borderzone infarcts cause contralateral hemianopia, sensory loss, and aphasia. Anterior borderzone infarcts (the territory between the middle cerebral and anterior cerebral arteries) result in contralateral weakness of the leg more than the arm, and spare the face. There may also be aphasia if the dominant hemisphere is affected (Ringelstein et al., 1983; Bogousslavsky and Regli, 1986; Bladin and Chambers, 1994). In contrast to embolic stroke, a hemodynamic stroke is often slowly progressive over several hours to days (Ringelstein et al., 1983). Hemodynamic stroke tends to have a poor prognosis (Bladin and Chambers, 1994).

Bogousslavsky and Regli (Bogousslavsky and Regli, 1986) studied watershed infarcts occurring in the anterior and posterior borderzones as well as the subcortical watershed region, delineated by CT scans. Syncope at onset and focal limb shaking were frequent. A high proportion of patients had hemodynamic internal carotid obstruction associated with a systemic precipitant, such as hypotension or increased hematocrit, which would contribute to impaired cerebral perfusion (Bogousslavsky and Regli, 1986). In patients with bilateral internal carotid occlusions, some patients have vertebrobasilar or presyncopal episodes due to hemodynamic insufficiency (Wade et al., 1987).

In a series of 300 consecutive patients with ischemic stroke, nearly 10% had hypotension at stroke onset, most of these having borderzone infarcts on CT scan (Bladin and Chambers, 1994). Most strokes were related to underlying cardiac disease or hypotension due to autonomic failure or antihypertensive therapy. Two-thirds of patients had associated moderate or severe carotid stenosis or occlusion. However, although borderzone infarcts are typically precipitated by hypotensive episodes, they can also be caused by microemboli, which can lodge preferentially in the cerebral watershed areas (Torvik and Skullerud, 1982; Momjian-Mayor and Baron, 2005).

Based on CT findings, Ringelstein et al. (Ringelstein et al., 1983) attempted to differentiate hemodynamic infarctions in borderzone regions affecting either the cortex or subcortical "terminal zone" infarcts from embolic infarctions. Bladin and Chambers (1993) identified confluent and partial internal watershed infarctions on CT scan, accounting for 6% of acute stroke admissions. Severe carotid occlusive disease and transiently impaired cardiac output were common in these patients. In an analysis of the NASCET dataset, subcortical internal borderzone infarcts were associated with higher degrees of arterial stenosis than perforating artery infarcts (Del Sette et al., 2000).

Hemodynamic cerebral infarcts may also be delineated by cerebral blood flow techniques such as single photon emission computed tomography (SPECT), positron emission tomography (PET), and transcranial Doppler with testing of vascular reserve (Weiller et al., 1991; Momjian-Mayor and Baron, 2005). Perfusion reserve and vasomotor reactivity were reduced in one study in patients with low-flow infarcts defined on CT and MRI, and yet were normal in patients with embolic territorial infarcts (Weiller et al., 1991). Unilateral borderzone infarcts were typically associated with internal carotid artery occlusion (Weiller et al., 1991). Diffusion and perfusion MRI are also helpful in determining embolic versus hypoperfusion substrates for borderzone infarction (Chaves et al., 2000; Momjian-Mayor and Baron, 2005).

35.5. Conclusion

The most common site for atheroma remains the bifurcation of the carotid artery for Caucasian stroke patients, but there are important racial variations. African-Americans, Asians, and Hispanics are more likely to have intracranial atherosclerosis. Aortic arch atheroma

is a more recently described site for large-artery atheroma, and it appears to be a major factor in stroke recurrence. Arch atheroma requires transesophageal echocardiography for diagnosis, and the optimal management remains unclear.

The mechanism of infarction resulting from large-artery atherosclerosis is usually artery-to-artery embolism. Atherosclerosis develops at the proximal site, and eventually plaque ulceration results in the formation of a platelet–fibrin thrombus. This thrombus may embolize to a distal site, resulting in the clinical features of the stroke. In a smaller proportion of stroke cases, the mechanism of infarction is thought to be due to hemodynamic mechanisms. This can be suspected when there are appropriate clinical features prior to onset (such as hypotension), a high-grade arterial stenosis, and a borderzone infarct on brain imaging.

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Chapter 36

Cardio-embolic stroke

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36.1. Cardio-embolic stroke overview

36.1.1. Epidemiology

Thrombus originating in or passing paradoxically through the left side of the heart, with subsequent embolization to and occlusion of an intracranial artery, accounts for 20–25% of all ischemic strokes. In addition to being common, cardio-embolic strokes are overall more severe than other subtypes of ischemic stroke, with greater morbidity and mortality. This greater clinical impact is presumably secondary to the association of cardiogenic emboli with occlusion of the large intracranial arteries (e.g., the basilar artery, middle cerebral artery, the carotid terminus), resulting in either significant posterior circulation injury (e.g., brainstem infarction, large cerebellar infarct with mass effect) or large-territory anterior circulation cortical strokes.

36.1.2. Etiologies

The underlying disease processes associated with cardiogenic embolic strokes can be grouped according to the underlying cardiac abnormality: diseases of the left atrium, the atrial septum, the left-sided heart valves (mitral and aortic), or the left ventricle (Table 36.1). Approximately half of all cardio-embolic strokes are caused by one specific disease, atrial fibrillation (AF), and much of this chapter will therefore highlight the current state of diagnosis and management of AF for the primary and secondary prevention of stroke. Controversial and evolving topics such as the association of atrial septal abnormalities (e.g., patent foramen ovale) with ischemic stroke are also covered in detail; less controversial topics, while no less important, are reviewed more generally (e.g., prosthetic cardiac valve disease).

36.1.3. Workup of possible cardio-embolic stroke

A thorough search for a potential cardiac source in patients with an unexplained large-vessel embolic stroke (e.g., those in sinus rhythm with no large artery disease) is imperative, as many of the common causes listed in Table 36.1 are often not readily apparent. The core evaluation includes rhythm monitoring and cardiac imaging studies. Rhythm monitoring, including electrocardiography, inpatient telemetry, and outpatient monitoring (e.g., Holter), is important as a screen for cardiac arrhythmias such as atrial fibrillation. Cardiac imaging studies (primarily echocardiography but also such evolving techniques as magnetic resonance imaging [MRI]) are critical for evaluating the many cardiac structural abnormalities associated with cardio-embolic stroke. As will be discussed throughout this chapter, transesophageal echocardiography is unquestionably superior to transthoracic echocardiography for this purpose. As a general rule, patients with unexplained large-vessel embolic stroke should undergo prolonged rhythm monitoring, at least during hospitalization, and have cardiac imaging, preferably with transesophageal echocardiography.

36.2. Atrial disease

36.2.1. Atrial fibrillation

Atrial fibrillation (AF), a supraventricular tachyarrhythmia in which the coordinated activation and contraction of the atria are perturbed, is one of the strongest known independent risk factors for ischemic stroke. Poorly organized contractions result in sluggish atrial blood flow, particularly within the left atrial appendage, thus establishing an optimal environment for thrombus formation. Embolization of thrombus to

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Table 36.1

Common potential causes of cardio-embolic stroke

Left atrial disease
Atrial fibrillation
Atrial myxoma
Atrial septal disease
Patent foramen ovale
Atrial septal aneurysm
Valvular disease
Mitral valve disease
Mitral stenosis
Mitral annular calcification
Mitral valve prolapse
Papillary fibroelastoma
Prosthetic valves
Infective endocarditis
Nonbacterial thrombotic endocarditis
Libman–Sacks endocarditis
Left ventricular disease
Acute myocardial infarction
Congestive heart failure
Left ventricular thrombus

the cerebral circulation produces vessel occlusion and ischemic stroke. Recent analysis of thrombo-embolic material recovered from acute stroke patients by endovascular mechanical thrombectomy suggests that these cardiogenic thrombo-emboli are largely composed of random deposits of fibrin and platelets (Marder et al., 2006).

The various etiologies of AF are typically divided into valvular and non-valvular disease processes; these two classifications will be addressed separately below. In addition, AF can be classified as either persistent (sustained, always present) or paroxysmal (intermittent, with varying time spent in normal sinus rhythm and in AF). While early studies suggested that paroxysmal AF might have a risk of stroke intermediate to that of normal sinus rhythm and persistent AF, currently available data suggest that the relative risk of stroke is similar in both forms. The following discussions of the epidemiology, etiology, associated risk factors for stroke, and the clinical trials of therapeutic options apply equally to both paroxysmal and persistent AF.

36.2.1.1. Non-valvular atrial fibrillation

36.2.1.1.1. Epidemiology

Non-valvular atrial fibrillation (NVAF) is the most common cardiac arrhythmia in the elderly, affecting approximately 2.5 million patients in the USA alone (Go et al., 2001). The prevalence of NVAF is strongly dependent upon age, occurring in approximately 0.1% in adults less than 55 years old, 5% in people over 65 years of age, and 10% in people over the age of 80. Overall, the median age of patients with NVAF is 72. NVAF is slightly more common in men than women, and prevalence is also higher in whites compared to blacks. Population estimates suggest that by the year 2050, almost 6 million Americans will have NVAF, with over half being older than 80 years of age.

36.2.1.1.2. Etiology/genetics

Most patients with NVAF have underlying structural heart disease related to ischemic coronary artery disease, congestive heart failure, or hypertension. The risk of developing NVAF secondary to structural heart disease appears to be heavily influenced by complex genetic factors, as it is more common in patients with a positive parental history of NVAF (Darbar et al., 2003; Fox et al., 2004). Polymorphisms of the genes encoding an angiotensin-converting enzyme (ACE), a cardiac gap junction protein (connexin 40) and a potassium channel subunit have all been identified as potentially important genetic modifiers of this risk (Wiesfeld et al., 2005). Concrete identification of such polymorphisms might ultimately help direct selected screening of high-risk patients in which the diagnosis is suspected yet unproven (i.e., patients with presumed paroxysmal NVAF).

A significant percentage of AF (10–25%) occurs in the absence of structural heart disease. This subset is typically referred to as "lone" AF. While some patients have a specific predisposing illness (e.g. hyperthyroidism), many occurrences of AF are idiopathic. Interestingly, up to one-third of patients with lone AF have a positive parental history of lone AF, and first degree relatives of patients with lone AF have a substantially increased risk of developing the disease as compared to population controls (Fox et al., 2004; Ellinor et al., 2005). Four distinct genetic mutations associated with familial lone AF have now been identified, and at least three additional loci have been found and await further characterization. All mutations described to date encode subunits of cardiac potassium channels, suggesting that many cases of familial lone AF are channelopathies (Roberts, 2006). Each of these autosomal dominant mutations encodes a gain-of-function subunit that results in a shortening of the atrial action potential duration and the effective atrial refractory period, providing a clear molecular predisposition to AF.

36.2.1.1.3. Overall stroke risk

Regardless of its etiology, NVAF is one of the strongest independent risk factors for stroke, producing a five-fold increased risk compared to healthy controls. In the absence of antithrombotic therapy to prevent

thrombus formation within the left atrium, the annual risk of stroke in all patients with NVAF approaches 5%, and this risk is modified by a number of risk factors. Overall, NVAF is responsible for 10–15% of all ischemic strokes and ~50% of all cardiogenic strokes (approximately 75,000 ischemic strokes annually in the USA). In patients older than 60, NVAF may account for up to one-third of all ischemic strokes.

36.2.1.1.4. Risk-stratification algorithms

The risk of stroke is not uniform across all patients with NVAF, but is instead heavily influenced by underlying co-morbid medical conditions. The importance of an accurate estimation of an individual patient's NVAF-associated stroke risk cannot be overstated, as the significance of this risk is typically the critical factor that directs the appropriate therapeutic intervention (discussed in detail in the following section). Initial insight into important modifying factors came from the landmark primary and secondary NVAF-related stroke prevention trials that began in the 1980s. In 1994, the Atrial Fibrillation Investigators (AFI) published a meta-analysis of five major primary prevention trials, identifying advancing age (relative risk [RR] = 1.4 per decade), previous transient ischemic attack (TIA) or stroke (RR = 2.5), hypertension (RR = 1.6) and diabetes (RR = 1.7) as independent risk factors for NVAF-associated stroke (Atrial Fibrillation Investigators, 1994a). Subsequent meta-analyses from the Stroke Prevention in Atrial Fibrillation (SPAF) trials (Anonymous, 1995, 1997) found advancing age (RR = 1.8 per decade), female gender (RR = 1.6), prior TIA or stroke (RR = 2.9), and hypertension (RR = 2.0) as independent stroke risk factors (Hart et al., 1999).

Although the AFI and SPAF meta-analyses were not in complete agreement, their observations provided an initial framework for estimating the NVAF-associated stroke risk of individual patients. Such algorithms have been validated and refined over time, with consensus recommendations published frequently by the American Heart Association (AHA) and the American College of Chest Physicians (ACCP). The 2004 ACCP guidelines (Singer et al., 2004) stratify NVAF patients into high, moderate, and low stroke risk groups based upon criteria summarized in Table 36.2.

The overall NVAF population distribution divides equally among the three strata: one-third each in the high-, moderate- and low-risk groups (Hart et al., 2003). Using the 2004 ACCP guidelines and data from the primary prevention trials mentioned above, the annual risk of stroke in untreated patients with NVAF is estimated to be 6–12% in the high-risk group, ~3% in the moderate risk group, and 1% in the low-risk group. A history of prior cerebral ischemia is an especially important risk factor, being much more strongly associated with increased stroke risk than other high-risk factors (note that the AFI and SPAF trials identified a RR for prior cerebral ischemia of approximately 2.5–2.9, as opposed to an RR for hypertension of 1.6–2.0). Compared to the 5% annual stroke risk seen in the overall NVAF patient population, patients with NVAF and prior cerebral ischemia have an annual stroke risk of approximately 12% (Anonymous, 1993).

Table 36.2

2004 ACCP Guidelines for risk stratification and antithrombotic guidelines for non-valvular atrial fibrillation

Risk category	Annual risk of stroke	Antithrombotic therapy
High[1]	6–12%	Warfarin, INR 2.0 to 3.0
Moderate[2]	~3%	Warfarin, INR 2.0 to 3.0 or aspirin
Low[3]	~1%	Aspirin

[1]High risk: *any* of the following: age > 75, prior cerebral ischemia (transient ischemic attack or stroke) or systemic embolism, hypertension, diabetes, congestive heart failure and/or moderately or severely impaired left ventricular systolic function.
[2]Moderate risk: age 65–75 and none of the high-risk clinical features.
[3]Low-risk: age < 65 and none of the high-risk features.
*In the absence of any antithrombotic therapy.

36.2.1.1.5. Influence of multiple high-risk factors

While the ACCP guidelines (and most others) rank patients with *any* of the high-risk factors as a high-risk patient, other classification schemes characterize the impact of *multiple* concurrent high-risk factors. Two such stratification schemes will be briefly reviewed—the $CHADS_2$ index and the Framingham risk score.

36.2.1.1.5.1. $CHADS_2$ index

The $CHADS_2$ index, built upon aspects of the AFI and SPAF algorithms, is a simple scale in which one point is assigned each to the presence of congestive heart failure, hypertension, age greater than 75, or diabetes mellitus and two points are assigned to a history of prior TIA or stroke. This index was tested, along with the AFI and SPAF algorithms, in a database of over 1,700 hospitalized Medicare beneficiaries aged 65–95 who were discharged with the diagnosis of NVAF and no treatment with warfarin (Gage et al., 2001). Approximately 30% of patients were treated with aspirin, with the remainder receiving no antithrombotic agent. Those patients with a $CHADS_2$ score of 0 (low-risk population) had an

adjusted stroke rate of 1.9 per 100 person-years. The stroke rate increased by a factor of 1.5 for each one of point increase on the $CHADS_2$ index, to approximately 6 per 100 person-years for a score of 3 and approximately 12 per 100 person-years for a score of 5. Interestingly, aspirin therapy was not associated with a significant reduction in stroke rate in this population (see also the discussion below). Overall, the $CHADS_2$ index had greater predictive accuracy of stroke risk than either the AFI or SPAF schemes.

36.2.1.1.5.2. Framingham risk score

A multivariate analysis of 705 Framingham Heart Study patients with new onset NVAF (and no history of cerebral ischemia) identified increasing age, increasing blood pressure, female gender, prior stroke or TIA, and diabetes as independent risk factors for stroke (Wang et al., 2003). A 31-point scale based upon these five risk factors was shown to be predictive of the 5-year risk of stroke.

Overall, both algorithms demonstrate that increasing numbers of risk factors are associated with increasing risk of NVAF stroke, thus allowing more precise estimations of the stroke-risk profile of individual patients. Ongoing evaluation, validation, and refinement of these and other detailed prediction algorithms will likely identify additional important risk modifiers.

36.2.1.1.6. Potential risk factors

Some additional risk factors merit discussion. Female gender and echocardiography findings are emerging as important stroke risk modifiers in NVAF patients, while the influence of hyperthyroidism on NVAF stroke risk now appears much lower than initially believed.

36.2.1.1.6.1. Female gender

The initial AFI and SPAF studies disagreed on the influence of female gender on stroke risk—this was a significant risk factor in the SPAF studies but not in the AFI meta-analysis. The $CHADS_2$ index, an amalgam of the *common* risk factors identified by the AFI and SPAF studies, does not include female gender as an important risk factor, while the Framingham risk score (which was based upon multivariate analysis of an observational cohort) does. The 2004 ACCP guidelines—perhaps the most influential and widely used risk stratification scheme—do not include female gender as a significant risk factor.

The Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study, a prospective cohort of over 13,500 NVAF patients, found that women have a statistically higher risk of thrombo-embolism than men (adjusted rate ratio of 1.6) (Fang et al., 2005). This effect was noted across all age groups as well as all stroke risk groups (e.g. high-versus low-risk). The authors of this study concluded that female gender is an independent risk factor of NVAF-associated stroke and should be considered in the stratification of high-risk patients.

36.2.1.1.6.2. Echocardiography

Transesophageal echocardiography (TEE) signs of abnormal atrial blood flow include low peak emptying velocities, spontaneous echo contrast and the presence of actual thrombus. These abnormalities, all of which are poorly evaluated with transthoracic echocardiography, appear to be associated with a two-fold to four-fold increased stroke risk in patients with documented NVAF (Anonymous, 1998). Future risk stratification schemes may thus be further refined by incorporating such TEE findings, but few if any schemes currently use this information. In addition, a normal TEE in a patient considered to be high risk by standard criteria might mitigate stroke risk. Several ongoing prospective studies are currently investigating the utility of TEE for the identification of such patients.

36.2.1.1.6.3. Thyroid disease

Approximately 10% of patients with hyperthyroidism develop NVAF, accounting for 2–5% of all NVAF cases (Squizzato et al., 2005). Several early studies suggested that hyperthyroidism-related NVAF was associated with an elevated stroke risk, but these studies have significant methodological flaws (reviewed by Singer et al., 2004). Currently available data do not support this association, and none of the major risk stratification schemes incorporate it as a risk factor. The risk of stroke in hyperthyroidism-associated NVAF appears to be adequately described by the stratification schemes mentioned above.

36.2.1.1.7. Treatment: the primary and secondary prevention of ischemic stroke in patients with NVAF—antithrombotic therapy

Multiple high-quality randomized controlled trials have investigated the efficacy of various antithrombotic agents in the primary and secondary prevention of NVAF-associated ischemic stroke. The landmark trials of the 1980s compared warfarin anticoagulation to no therapy, aspirin to no therapy, and warfarin anticoagulation to aspirin. The results of these trials have been evaluated in several meta-analyses (Anonymous, 1994a; Hart et al., 1999; van Walraven et al., 2002; Aguilar and Hart, 2005), validated in numerous subsequent studies (Gage et al., 2001; Wang et al., 2003), and reviewed extensively elsewhere (Ferro, 2003; Singer et al., 2004). The major findings of these and other relevant studies are summarized below.

36.2.1.1.7.1. Warfarin versus no therapy

Multiple studies have demonstrated the superiority of adjusted-dose warfarin anticoagulation over no antithrombotic therapy. In five major primary prevention trials (Petersen et al., 1989, Anonymous, 1990, 1991b; Connolly et al., 1991; Ezekowitz et al., 1992), adjusted-dose warfarin, with a target international normalized ratio (INR) of 2–3, reduced the annual rate of stroke in all NVAF patients from 4.5% in the untreated population to 1.4% in the anticoagulation population—a relative risk reduction of 68%. (It is telling to note that all of these trials were terminated early, at their interim analyses, because of the dramatic benefit of warfarin.) The "number needed to treat" to prevent one stroke was 32—for every 1,000 patients treated, 31 ischemic strokes would be prevented per year. In addition, warfarin therapy (compared to no treatment) reduced the combined outcome of stroke, systemic embolism or death by 48%, and all-cause mortality by 33%.

Warfarin anticoagulation is also equally effective in preventing *recurrent* NVAF-associated stroke (i.e., secondary prevention). In the European Atrial Fibrillation trial, the only placebo-controlled secondary stroke prevention trial for NVAF, warfarin anticoagulation reduced the annual risk of recurrent stroke from 12% in the untreated control group to 4% (Anonymous, 1993). This corresponds to a relative risk reduction of 66%, similar to the risk reduction seen in the primary prevention trials. The "number needed to treat" for secondary prevention from this trial was 13.

Intracranial hemorrhage, the most feared complication of chronic anticoagulation therapy, was not significantly increased in any of the studies which compared adjusted-dose warfarin with no therapy. The annual rate of major bleeding was 1.0% in control patients and 1.3% in warfarin patients; the annual rates of intracranial hemorrhage in control and warfarin-treated groups were 0.1% and 0.3%, respectively.

36.2.1.1.7.2. Aspirin versus no therapy

Several randomized controlled trials have compared the efficacy of aspirin versus no antithrombotic therapy in the prevention of NVAF-associated stroke. An initial meta-analysis (Anonymous, 1997a) of five early trials found a relative risk reduction of 21% for aspirin therapy (as compared to a relative risk reduction [RRR] of 68% for warfarin versus no therapy). These results, however, were only marginally significant (95% confidence intervals of 0–38%). Aspirin therapy was not associated with an increased risk of major bleeding complications, including intracranial hemorrhage. Subsequent meta-analyses have noted similar findings, with the RRR of ischemic stroke averaging around 25%. Based upon these data, treating 1,000 NVAF patients for 1 year with aspirin would prevent around 10 ischemic strokes.

The recently published Japan Atrial Fibrillation Stroke Trial (JAFST) has cast doubt on the efficacy of aspirin therapy in preventing NVAF-related thrombo-embolic events, at least in the Japanese population (Sato et al., 2006). This study randomized over 800 NVAF patients without a recent history of cerebral ischemia to either aspirin therapy or no treatment. The study population was heterogeneous, with almost half being high-risk patients. The trial was terminated early after an interim analysis found no benefit of aspirin therapy for the prevention of ischemic strokes, and also noted a marginally significant increase in the rate of major bleeding events.

36.2.1.1.7.3. Warfarin versus aspirin

Several randomized controlled trials have compared adjusted-dose warfarin and aspirin for stroke prevention in NVAF (Petersen et al., 1989; Anonymous, 1993, 1994b; Gullov et al., 1998; Hellemons et al., 1999). A meta-analysis of these trials demonstrated that adjusted-dose warfarin therapy is unquestionably more protective than aspirin, with a relative risk reduction of 52% (van Walraven et al., 2002). Of note, major bleeding (intracranial or serious systemic hemorrhage) was increased by 1.7-fold in the warfarin group; roughly 22% of these episodes were intracranial hemorrhages. Despite the increased risk of bleeding, the overall benefit of warfarin remained clear—for every 1,000 NVAF patients treated with warfarin instead of aspirin for 1 year, 23 ischemic strokes would be prevented at the cost of 9 major bleeds (2 of which would be intracranial hemorrhage).

36.2.1.1.7.4. Summary of antithrombotic trials

Multiple studies have demonstrated that warfarin anticoagulation is superior to either aspirin therapy or no treatment, and that aspirin is, at best, only marginally better than no antithrombotic therapy. Head-to-head comparison of warfarin and aspirin confirmed an overall benefit of warfarin, even in light of a slightly increased risk of intracranial hemorrhage. The 2004 ACCP guidelines for NVAF-related stroke prevention conclude that the "evidence for the efficacy of anticoagulation in atrial fibrillation is strong, consistent, and based upon high-quality studies," while the data supporting the efficacy of aspirin is "substantially weaker."

36.2.1.1.7.5. Optimal intensity of anticoagulation

The goal of preventing ischemic strokes with warfarin anticoagulation must be balanced against the risk of debilitating systemic bleeding complications, especially intracranial hemorrhage. With this in mind, two critically important observations can be made about the optimal intensity of warfarin anticoagulation in NVAF

patients. First, several early stroke prevention trials demonstrated that low-intensity warfarin therapy (target INRs of 1.1–1.6), even in combination with aspirin, was markedly inferior to adjusted-dose warfarin (target INR of 2–3) in preventing ischemic stroke (Anonymous, 1996; Gullov et al., 1998). These and other studies suggest that the combination of low-intensity warfarin with aspirin does not provide any benefit over aspirin therapy alone. Recent observational studies have demonstrated that monotherapy with warfarin that produces an INR of less than 2 is likely to be inferior to even the marginal benefit of aspirin, with a risk of ischemic stroke that approaches that of NVAF patients not taking any antithrombotic medications (Hylek et al., 2003). Consistent with these observations are reports that the majority of ischemic strokes in NVAF patients taking adjusted-dose warfarin with a *target* INR of 2–3 actually occur at ratios of less than 2; that is, most warfarin "failures" are due to subtherapeutic dosing of warfarin and not to thromboembolism that occurs despite adequate anticoagulation. Interestingly, while true "warfarin failures" do occur (i.e., despite an INR of 2–3), such ischemic strokes appear to be less severe than those that occur at subtherapeutic ratios, with a decrease in both 30-day mortality and the likelihood of survival with major disability (Hylek et al., 2003). Overall, adjusted-dose warfarin (target INR of 2–3), compared to either low-intensity warfarin or aspirin alone, reduces not only the *frequency* but also the *severity* of ischemic stroke.

Second, several randomized trials and community-based observational studies have shown that adjusted-dose warfarin with a target INR of 2–3 can be implemented without a dramatic increase in intracranial hemorrhage or other serious bleeding complications (van Walraven et al., 2002; Jones et al., 2005). Importantly, the increased risk of intracranial hemorrhage attributable to adjusted-dose warfarin therapy is primarily associated with supratherapeutic anticoagulation levels (INR $>$ 3.5–4.0). An observational cohort study of over 13,000 patients with NVAF found that the risk of intracranial hemorrhage in patients with INR levels between 2.0 and 3.9 was no different than the risk seen in patients with INR levels between 1.0 and 1.9 (roughly 0.3–0.6 intracranial hemorrhages per 100 person-years). The risk of intracranial hemorrhage, however, increased significantly with INRs greater than 4, to 2.7 intracranial hemorrhages per 100 person-years with INRs 4.0–4.5, and 9.4 intracranial hemorrhages per 100 person-years with INRs $>$ 4.5 (Hylek et al., 2003). Other studies have also found a similar "threshold" INR level (greater than 3.5–4.0) at which the risk of warfarin-related intracranial hemorrhage begins to rise dramatically (Fang et al., 2004a).

In summary, numerous high-quality randomized trials and observational studies have shown that the optimal intensity of adjusted-dose warfarin in NVAF patients is a target INR of 2–3. This narrow therapeutic window appears to provide maximal protection against ischemic stroke with the minimal risk of intracranial hemorrhage. Two important observations are: (1) INRs of less than 2 are ineffective, being associated with more frequent and severe ischemic strokes (perhaps equivalent to withholding all antithrombotic therapy); and (2) INRs $>$ 3.5–4.0 are associated with a significant increase in the risk of intracranial hemorrhage. These observations suggest that rigorous monitoring of the INR and careful adjustment of warfarin dosing are critical for the prevention of both NVAF-related ischemic stroke (warfarin "failures" from subtherapeutic anticoagulation) and treatment-related intracranial hemorrhage (from "supratherapeutic" warfarin dosing).

36.2.1.1.7.6. Selecting antithrombotic therapy in NVAF patients

The selection of an antithrombotic agent for stroke prevention in NVAF patients must weigh the stroke risk of *individual* patients against the known risks and efficacy of the therapy. The 2004 ACCP guidelines, perhaps the most commonly used, recommend anticoagulation with an oral vitamin K antagonist such as warfarin (adjusted-dose, with a target INR range of 2–3) for *all* high-risk patients. In moderate-risk NVAF patients, either adjusted-dose warfarin or aspirin is considered a reasonable choice. In this scenario, emerging risk factors such as female gender or abnormal echocardiography findings might elevate warfarin to the optimal choice, although this remains unproven. Finally, for low-risk factors, aspirin is recommended as the optimal treatment. This weighs the very low-risk of stroke in this population (likely around 1% per year) against the known risks of anticoagulation and aspirin therapy. Interestingly, some guidelines suggest that zero antithrombotic therapy is also reasonable in this population, reflecting the marginal benefit aspirin provides and its low but non-trivial potential for adverse bleeding events.

36.2.1.1.7.7. Underutilization of anticoagulation in NVAF patients

The incidence of NVAF-associated ischemic stroke has decreased steadily over the last 20 years, a trend that correlates directly with increased use of anticoagulation therapy (Fang et al., 2004b; Miyasaka et al., 2005; Friberg et al., 2006). Despite this clear improvement, up to half of all high-risk patients are not prescribed this treatment. The reasons for underutilization are many, but include (1) difficulty of use, (2) likely

underestimation of the true benefit versus true risk of anticoagulation by both physicians and patients, and (3) physician bias (Bungard et al., 2000).

Warfarin therapy is notoriously burdensome for both the physician and patient. The therapeutic window is narrow, and multiple dietary and drug interactions influence its potency, necessitating frequent monitoring and dose adjustments. Despite careful monitoring, patients are outside of the target INR range 30–50% of the time, with half being below the target range and half being above (Jones et al., 2005). Finally, many patients make undesired lifestyle adjustments to avoid behaviors that might increase risk of trauma-related hemorrhage. These factors influence many physicians and NVAF patients to opt against warfarin therapy. In addition, many physicians and patients appear to underestimate the benefit of anticoagulation and to overestimate the associated risks, leading many to avoid its use on the presumption of safety. As previously noted, anticoagulation reduces the individual as well as societal burden of stroke disability by both preventing and mitigating ischemic stroke injury. In particular, the mitigation of ischemic stroke injury has likely not been adequately factored into the risk–benefit algorithms that physicians utilize to risk stratify individual patients, suggesting that the potential gain from anticoagulation therapy is much higher than appreciated (Miller et al., 2005).

Physicians also appear to overestimate the risk of warfarin use, and are particularly influenced by experiences with such adverse events. A recent study found that physicians treating NVAF patients with a warfarin-related hemorrhage were less likely to prescribe warfarin to subsequent NVAF patients (Choudhry et al., 2006). Interestingly, physicians treating patients with an NVAF-related ischemic stroke who were not taking warfarin were not more likely to prescribe anticoagulation to subsequent NVAF patients. Thus, despite excellent data demonstrating the overall net benefit of anticoagulation, individual physician experiences often reinforce concerns regarding its safety but not necessarily its efficacy.

Ironically, when presented with the relative risks, most patients value the reduction in ischemic stroke risk over the increased risk of hemorrhage. Unfortunately, many NVAF patients have a very poor understanding of their disease, particularly in regard to their risk of thrombo-embolism and the risks and benefits of anticoagulation. Several studies have found that 40–50% of all patients with NVAF are unaware of their cardiac condition and its association with cardio-embolic stroke; up to 40% of patients taking warfarin are unaware of the reason for its use (Lip et al., 2002; Lane et al., 2006). Surprisingly, over half believe that their condition is not serious. These observations suggest that many NVAF patients may decline anticoagulation therapy, especially when told of its potential risk, simply because they fail to appreciate the full nature and risk of their disease.

Finally, the influence of potential physician bias on the underutilization of anticoagulation in two specific patient populations—female patients and patients ages 75 years or older—should be addressed. Several studies have demonstrated that female NVAF patients of all age groups are less likely to be prescribed anticoagulation than male patients, including those with prior thrombo-embolism (Humphries et al., 2001; Friberg et al., 2006). Whether this is a physician bias or patient-based preference is unclear, but the observation that female gender may be an independent risk factor for NVAF-associated stroke suggests that this discrepancy needs to be further evaluated and addressed.

Increasing age is one of the strongest modifiers of NVAF stroke risk, with most patients older than 75 being at especially high risk. Despite this, and because of the concern over bleeding complications, patients older than 75 years of age are actually less likely to be prescribed anticoagulation than younger patients (Antani et al., 1996). If warfarin is utilized, a low-intensity INR (e.g., 1.5–2.0) is often targeted, a practice advocated by one recently published guideline (Fuster et al., 2001). A wealth of data, however, now demonstrate that these patients in particular are likely to benefit the most from adjusted-dose warfarin with a target INR range of 2–3, without the presumed increased risk of complications. While increase age is associated with risk of intracranial hemorrhage, this risk appears to be most significant in patients greater than 85 years of age (Fang et al., 2004a).

36.2.1.1.7.8. Possible alternatives to oral vitamin K antagonists

Warfarin is currently the best therapy available for stroke prevention in high-risk NVAF patients, even when the risks and difficulties with implementation are considered. These concerns, combined with physician biases and poor patient education, nonetheless strongly influence both physician and patient attitudes towards long-term warfarin use and no doubt contribute to its underutilization. It is thus encouraging to note that multiple potential alternatives to warfarin therapy are currently being investigated. The goal, of course, is to identify a treatment option that combines the therapeutic benefit of warfarin with ease of use (preferably fixed-dose, with no need to monitor the level of anticoagulation) and an improved safety profile. Therapies currently being evaluated include direct thrombin inhibitors, factor Xa inhibitors, dual antiplatelet combinations and surgical/endovascular left atrial appendage closure. Each of these will be discussed briefly below.

36.2.1.1.7.8.1. Direct thrombin inhibitors Anticoagulation with direct pharmacologic inhibition of thrombin is an exciting possible alternative to warfarin therapy. Two oral direct thrombin inhibitors (DTIs) are currently being studied (ximelagatran and dabigatran), and their potential advantages over warfarin are substantial (Gustafsson, 2003; Weitz and Bates, 2005). Both can be given as a fixed daily dose, without need for monitoring of anticoagulation levels. Neither appears to have significant food or cytochrome p450-related drug interactions, and both are eliminated primarily via the kidneys. Most importantly, these DTIs appear to have a broader therapeutic margin than warfarin, allowing for a possible improved safety profile without loss of efficacy.

The SPORTIF (Stroke Prevention using an Oral Thrombin Inhibitor in Atrial Fibrillation) trials compared the efficacy of ximelagatran to warfarin for prevention of stroke or systemic embolism in high-risk NVAF patients. In the SPORTIF V study—a large, phase III, randomized, double-blind trial (Olsson, 2003)—3,922 high-risk NVAF patients were randomized to receive either adjusted-dose warfarin (target INR range 2–3) or fixed-dose oral ximelagatran (36 mg twice daily). The primary end-point was all strokes (ischemic or hemorrhagic) and systemic embolic events, and the trial was designed to test the non-inferiority of ximelagatran. The primary event rate was 1.6% per year for ximelagratan and 1.2% per year for warfarin, supporting the non-inferiority of the DTI. Importantly, no difference was noted in major bleeding between the two, though total bleeding (major and minor events) was significantly lower with ximelagatran.

While the SPORTIF trials are proof of principle that DTIs may be an excellent alternative to warfarin therapy, ximelagatran itself has yet to be approved for use in the USA given concerns for possible hepatotoxicity. In SPORTIF V, serum alanine aminotransferase levels increased more than three times the upper limit in 6% of patients, and one case of fatal liver disease was documented. Thus, while promising, ximelagatran is not a treatment option for NVAF patients at the time of this writing. A phase III, randomized, double-blind trial of a second oral DTI, dabigatran, is currently underway in high-risk NVAF patients. This trial (the RE-LY study) intends to enroll up to 15,000 patients and has a target completion date of September 2009.

36.2.1.1.7.8.2. Factor Xa inhibitors Subcutaneous low molecular weight heparinoids (LMWHs) produce systemic anticoagulation primarily by inhibiting factor Xa (Weitz and Bates, 2005). These compounds have been extensively studied in the prevention of venous thrombo-embolism, and are also used as short-term bridging therapy to chronic warfarin anticoagulation. The typical twice-daily subcutaneous dosing schedule of most LMWH compounds precludes their consideration as a long-term alternative to warfarin. One LMWH, idraparinux, has a substantially longer duration of action than most, allowing for once weekly subcutaneous dosing. This compound has recently been compared to warfarin in a phase III, open-label trial in high-risk NVAF patients (the AMADEUS study); the trial has been completed, but the results have not been published at the time of writing. A positive trial might identify idraparinux as an excellent alternative to warfarin therapy, and prompt further interest in the ongoing development of oral factor Xa inhibitors.

36.2.1.1.7.8.3. Dual antiplatelet therapy The hypothesis that combination antiplatelet therapy might be as efficacious as warfarin, while providing greater ease of use and an improved safety profile, has recently been tested. One arm of the ACTIVE trial (Atrial Fibrillation Clopidogrel Trial with Irbesartan for the Prevention of Vascular Events) was an open comparison of adjusted-dose warfarin versus the combination of aspirin and clopidogrel in patients with NVAF. While these results have yet to be officially published, preliminary data presented in abstract form suggest that this trial was terminated early after an interim analysis showed a clear benefit of warfarin (Cleland et al., 2005). If these observations hold, they will provide yet more evidence that anticoagulation is unquestionably superior to antiplatelet therapy for stroke prevention in NVAF patients. Whether dual antiplatelet therapy is superior to monotherapy with aspirin in NVAF patients unable to take warfarin is being studied in an ongoing separate arm of the ACTIVE trial.

36.2.1.1.7.8.4. Left atrial appendage occlusion Ninety percent of all atrial thrombi in NVAF patients form in the left atrial appendage (Aberg, 1969; Stoddard et al., 1995). Obliteration of the left atrial appendage by either surgical or endovascular means might dramatically reduce thrombus formation and subsequent embolism; such an approach might be especially appealing for patients with contraindications to anticoagulation therapy, particularly in light of the marginal benefit of antiplatelet therapy. A recent feasibility study demonstrated that a percutaneous transcatheter occlusion device could be successfully deployed in 108 out of 111 high-risk NVAF patients who had contraindications to warfarin therapy (Ostermayer et al., 2005), though no clear long-term conclusions regarding long-term stroke prevention can be drawn. While promising, such devices need to be rigorously tested

against the known risks and benefits of available antithrombotic therapies before their routine use can be recommended.

36.2.1.1.7.9. Special situations

36.2.1.1.7.9.1. True warfarin failures Most ischemic strokes in NVAF patients taking warfarin occur at subtherapeutic INRs; rarely, an NVAF-related ischemic stroke occurs despite a therapeutic INR (Hylek et al., 2003; Singer et al., 2004). The first approach is of course to confirm that the stroke in question is likely cardiogenic in nature (e.g., not secondary to carotid atherosclerosis or small vessel disease). Whether increasing the target INR (e.g., 2.5–3.5) or adding an antiplatelet agent for true failure is reasonable from a risk-benefit analysis is unclear, but circumstantial data suggest that adding an antiplatelet agent may be safest. Increasing the target INR will likely increase the time spent with INRs above the threshold of elevated intracranial hemorrhage risk (>3.5–4.0). Antiplatelet therapy with warfarin, on the other hand, is already advocated by some guidelines for NVAF patients with underlying coronary artery disease (Antman et al., 2004). Finally, some experts advocate investigating the coexistence of underlying hypercoagulable states, and at least one study (Poli et al., 2005) found evidence that elevated homocysteine levels might be important in such "warfarin failures."

36.2.1.1.7.9.2. Initiating anticoagulation following NVAF-related ischemic stroke Very limited data are available to help guide the appropriate timing of initiating anticoagulation therapy in NVAF patients with acute ischemic stroke, and the concern of hemorrhagic transformation must be weighed against the risk of recurrent thrombo-embolism. The Heparin in Acute Embolic Stroke Trial (HAEST) randomized 449 patients with NVAF-related embolic stroke to either subcutaneous low-molecular weight heparin (dalteparin) or aspirin within 30 hours of stroke onset. No benefit in preventing recurrent stroke within 14 days was found, and the frequency of symptomatic intracranial hemorrhage was similar (Berge et al., 2000). The European Atrial Fibrillation Trial began oral anticoagulation within 14 days of stroke in most patients (without bridging therapy with heparin) and had no significant adverse events (Anonymous, 1993). The recent stroke prevention guidelines of the American Heart Association/American Stroke Association advocate initiating anticoagulation therapy within 2 weeks of a NVAF-related TIA or stroke, except in cases of large ischemic injury or poorly controlled hypertension, but do not comment on the acute use of anticoagulation with heparin (Sacco et al., 2006).

36.2.1.1.7.9.3. Resuming anticoagulation following warfarin-related intracranial hemorrhage The decision to resume anticoagulation after a warfarin-related intracranial hemorrhage must weigh the risk of recurrent intracranial hemorrhage against the risk of NVAF-related thrombo-embolism. While little data are available to inform this risk, long-term anticoagulation likely remains the best choice, especially if a modifiable precipitating factor (e.g., poorly controlled hypertension, over-anticoagulation, trauma) is identified and addressed. This decision is particularly difficult, however, in clinical scenarios with fixed risks of hemorrhage and thrombo-embolism (e.g., coexisting cerebral amyloid angiopathy and NVAF).

36.2.1.1.7.9.4. NVAF following cardiac surgery The incidence of NVAF following coronary artery bypass grafting can be as high as 40%, with most cases occurring within 5 days of surgery (Singer et al., 2004). While greater than 90% of patients resume sinus rhythm by the eighth post-operative week, the short-term risk of NVAF-related embolic stroke is significant. The 2004 ACCP guidelines recommend adjusted-dose warfarin with a target INR range of 2–3 for those patients with NVAF that persists for more than 48 hours, with discontinuation "several weeks" after sinus rhythm has been re-established. This patient population obviously may have significant bleeding risks, and such treatment must thus be made carefully on an individual basis. Interestingly, several prospective studies are currently investigating the impact of elective occlusion of the left atrial appendage in patients undergoing coronary artery bypass grafting (Crystal et al., 2003; Healey et al., 2005). Whether such treatment decreases the risk of thrombo-embolism or the need for anticoagulation or antiplatelet therapies for post-operative NVAF remains to be established.

36.2.1.1.7.9.5. Cardioversion for NVAF The need of anticoagulation for NVAF patients undergoing either elective or chemical cardioversion is typically based upon the known duration of the arrhythmia (Singer et al., 2004). Patients with NVAF of greater than 2 days duration are often treated with warfarin anticoagulation for 3 weeks prior to and 4 weeks following conversion. An alternative strategy has emerged in which anticoagulation is started for several days and transesophageal echocardiography is then performed to evaluate for the presence of left atrial thrombus. Patients without thrombus undergo cardioversion followed by 4 weeks of warfarin, while patients with identifiable clot have warfarin continued for several weeks, postponing cardioversion until documented clot resolution (Klein et al., 2001, 2006).

For patients with NVAF of less than 2 days duration, cardioversion is often carried out in the absence

of anticoagulation, though many guidelines recommend that empiric anticoagulation with heparin be given at presentation and until cardioversion is completed. Many experts, however, argue that screening TEE is appropriate, primarily given the concern that these patients may have had prior episodes of asymptomatic paroxysmal atrial fibrillation. The necessary duration of anticoagulation following successful cardioversion of either scenario remains unclear and must be decided on an individual basis. The primary issue is whether patients truly maintain sinus rhythm or instead have periods of paroxysmal atrial fibrillation. Patients with more than one prior episode of AF should likely be considered to have chronic paroxysmal NVAF, even following successful cardioversion.

36.2.1.1.7.9.6. Rate versus rhythm control Several studies (Van Gelder et al., 2002; Wyse et al., 2002) have compared long-term outcomes of rate control strategies (tolerating atrial fibrillation but preventing rapid ventricular response tachycardia with nodal blocking agents) to rhythm control strategies (cardioversion followed by anti-arrhythmic medications). In short, ischemic events occur at similar rates in both rate and rhythm control strategies, with most strokes occurring in patients off anticoagulation or with subtherapeutic INRs. The failure of rhythm control strategies to decrease cardiogenic strokes is likely explained by the poor rate of long-term maintenance of sinus rhythm—40–50% of patients have recurrent AF at 1 year.

Several invasive procedures for restoring sinus rhythm in NVAF patients are being investigated. These include endovascular ablation techniques (e.g., circumferential pulmonary vein ablation (Oral et al., 2006)) and cardiac surgical procedures (e.g., the "maze" procedure (Barnett and Ad, 2006)). While promising, currently available options have yet to demonstrate long-term maintenance of sinus rhythm without intervening periods of paroxysmal NVAF. While it is possible that such procedures may produce durable rhythm control and ultimately negate the need for anticoagulation, the most prudent course at present is to choose antithrombotic therapy based upon the assumption that the patient has paroxysmal AF.

36.2.1.1.7.9.7. Chronic atrial flutter or the sick sinus syndrome The risk of stroke from chronic atrial flutter is difficult to determine, largely because of the rare nature of this arrhythmia. Many cases of atrial flutter, however, have associated periods of atrial fibrillation, and most guidelines recommend choosing antithrombotic therapy for atrial flutter patients based upon algorithms for NVAF patients (Singer et al., 2004). Sick sinus syndrome is a sinus nodal disease characterized primarily by episodic and often severe bradycardia. Paroxysmal NVAF may be present in up to 40% of sick sinus syndrome patients, and may therefore be the underlying cause of an otherwise unexplained embolic stroke (Greenspon et al., 2004). Anticoagulation therapy is often advocated for secondary stroke prevention in sick sinus syndrome patients, even without documented paroxysmal NVAF; the appropriate antithrombotic therapy for primary prevention remains unclear.

36.2.1.1.8. Treatment: the primary and secondary prevention of ischemic stroke in patients with NVAF—antihypertensive therapy

Most of the focus of stroke prevention in NVAF patients has centered upon antithrombotic therapy. Control of associated high-risk factors, especially hypertension, also appears to be very important. Hypertension-related left ventricular diastolic dysfunction increases left atrial appendage stasis and thus increases the potential for thrombus formation. A recently published study demonstrated that improved blood pressure control was associated with a significant decrease in stroke in NVAF patients, a reduction that was independent of anticoagulation use (Arima et al., 2005). Given these results and the overwhelming evidence supporting the many benefits of blood pressure control in general, aggressive hypertensive control should be advocated in most if not all NVAF patients.

36.2.1.1.9. Detection of paroxysmal atrial fibrillation

As NVAF is often paroxysmal in nature, it is possible for patients to be in sinus rhythm at the time of their ischemic stroke. The suspicion for the paroxysmal form of NVAF, then, often arises in the context of an embolic large vessel stroke in a patient with classic risk factors for NVAF and no identifiable source of thromboembolism (e.g., no evidence of significant extracranial or intracranial atherosclerotic disease or other embolic source such as dissection). Patients with such cryptogenic strokes typically undergo echocardiography as well as prolonged rhythm monitoring in an effort to detect a cardiac source of thrombus or episodes of paroxysmal NVAF.

36.2.1.1.9.1. Echocardiography

All patients with unexplained embolic stroke should undergo echocardiography to investigate the multiple potential cardiac sources of thrombo-embolism that are discussed throughout this chapter. Transesophageal echocardiography remains the gold standard for this evaluation (Harloff et al., 2006). While not definitive proof of undetected paroxysmal NVAF, TEE findings

of left atrial clot, low peak emptying velocities, left atrial enlargement, or spontaneous echo contrast might increase the clinical suspicion of this form of NVAF and direct further investigation (e.g., with prolonged rhythm monitoring). With the exception of documented left atrial thrombus, whether many of these echocardiography findings in the absence of documented NVAF are independent risk factors for cardio-embolic stroke remain to be determined.

36.2.1.1.9.2. Prolonged rhythm monitoring

Short-term outpatient ambulatory electrocardiography monitoring (24-hour Holter monitoring) is unlikely to be useful for detecting paroxysmal NVAF (Schaer et al., 2004). In addition, early-generation "event monitors" required patients to have symptomatic episodes of paroxysmal NVAF in order for the arrhythmia to be captured on the recording device; as most episodes appear to be asymptomatic, these devices are also unlikely to be helpful. Fortunately, current event monitors can now detect asymptomatic episodes of paroxysmal NVAF and can be worn for up to 30 days at a time. While such technology may be extraordinarily useful in selected patient populations (e.g., the patient with cryptogenic embolic large-vessel stroke), the utility and cost-effectiveness of such monitors to detect paroxysmal NVAF has not been extensively studied.

36.2.1.2. Valvular atrial fibrillation (VAF)

Early observational studies demonstrated that patients with atrial fibrillation associated with valvular disease (e.g., mitral valve stenosis, prosthetic valve) have an extremely high risk of cardiogenic stroke and systemic embolism. As such, these patients were excluded from most of the stroke prevention treatment trials discussed above. Most guidelines recommend systemic anticoagulation for all patients with valvular atrial fibrillation, with the optimal intensity of anticoagulation determined by the particular valvular abnormality. This is discussed in detail in a subsequent section on valvular disease (Section 36.4).

36.2.1.3. Atrial myxoma

Atrial myxoma, the most common primary cardiac tumor, is a rare but treatable cause of cardiogenic stroke. Most arise within the left atrium and present with either constitutional symptoms of malignancy, cardiac dysfunction, or systemic embolism. The most common neurological presentation of atrial myxoma is stroke, though seizures and psychiatric syndromes have also been reported. While up to 80% of stroke is ischemic secondary to embolism, 20% of patients present with intraparenchymal or subarachnoid hemorrhage (reviewed by Ekinci and Donnan, 2004).

Cardio-embolic ischemic stroke from atrial myxoma is due to either thrombus formation on the tumor surface, followed by embolization, or direct embolization of tumor fragments. Tumor fragment embolization is the most likely mechanism, particularly given its documented association with intracranial hemorrhage (Burton and Johnston, 1970). Distal embolization of atrial myxoma fragments can lead to local blood vessel invasion by tumor cells, with subsequent development of fusiform aneurysms. As opposed to classic saccular aneurysms of the circle of Willis, myxoma-associated aneurysms are frequently multiple in number and distal in location, often mimicking "mycotic" aneurysms (Gonsalves and Nidecker, 1979). Rupture of these atypical aneurysms can produce subarachnoid hemorrhage, intraparenchymal hemorrhage, or both. Rare cases of malignant tumor growth within the adjacent brain tissue have also been reported (Budzilovich et al., 1979).

Most atrial myxomas are readily detectable as mobile atrial masses by routine echocardiography. As the workup for unexplained embolic stroke should include echocardiography, the identification of myxomas, while rare, is fairly straightforward. Current standard echocardiography techniques approach 100% sensitivity for these tumors, though false negatives have been reported (Thompson et al., 1988).

The definitive treatment of an atrial myxoma is surgical resection. For patients who are not candidates for surgery, the relative risks and benefits of antiplatelet or anticoagulation therapy are unknown. The known association with aneurysm formation and intracerebral hemorrhage should be considered before anticoagulation therapy is initiated. The optimal treatment of myxoma-related aneurysms is also unclear, and few cases in the literature are available to guide management.

36.3. Atrial septal disease

Interatrial septal abnormalities such as patent foramen ovale (PFO) and atrial septal aneurysm are common, occurring in approximately 25% of the general population. Whether or not such abnormalities may be associated with cardiogenic stroke has been debated for some time. Proponents suggest that cerebral emboli arise either from venous thrombi that traverse a PFO and paradoxically embolize to the cerebral circulation or from embolization of thrombi that develop within the PFO itself. The following sections review the anatomy of interatrial septal abnormalities and the literature that supports their association with cryptogenic embolic stroke in younger patients.

36.3.1. Anatomy of interatrial septal abnormalities

In the fetal circulation, the foramen ovale allows maternally oxygenated blood to bypass the non-functioning fetal lungs via a right-to-left shunt through the atrial septum. The interatrial septum and the foramen ovale derive embryologically from the fusion of two distinct septae (Fig. 36.1). The septum primum forms first, growing downward from the roof of the primitive common atrium, ultimately fusing with the interventricular septum; a small ostium (the foramen secundum) then arises in its superior portion (Fig. 36.1A-D). The septum secundum, originating to the right of the septum primum, subsequently forms. The septum secundum also has a residual ostium (the foramen ovale), but it is located in its inferior portion (Fig. 36.1E, F). The two foramina thus do not overlap, a feature that allows for future closure of the shunt.

In utero, blood returning via the inferior vena cava is directed towards the foramen ovale by the Eustachian valve, a venous valve located at the junction of the inferior vena cava and right atrium. Blood then passes through the foramen ovale, travels upwards between the two septae, and enters the left atrium via the foramen secundum (Fig. 36.1F). Left atrial pressures increase at birth, sealing the septae together, preventing further interatrial blood flow. If closure does not occur, however, a potential interatrial connection remains.

When identified postnatally, these structures are classified as interatrial septal abnormalities. A PFO refers to an intact interatrial connection through the foramen ovale, the two septae and the foramen secundum. Its size is defined as the maximum separation between the two septae seen during the cardiac cycle. An atrial septal aneurysm is somewhat of a misnomer, and is more accurately described as a hypermobile septum primum, specifically its inferior portion that covers the foramen ovale. Hypermobility of this portion of the septum primum can lead to its alternating protrusion into the atria during the cardiac cycle. Most studies define an atrial septal aneurysm as a septum that bulges more than 10 mm into the atria.

36.3.2. Prevalence and detection of interatrial septal abnormalities

Autopsy studies of normal human hearts have estimated the prevalence of a PFO in the general population to be from 20% to 35%, with an average of approximately 26% (Wright et al., 1948; Hagen et al., 1984; Windecker and Meier, 2002). The prevalence of atrial septal aneurysms is less well described but appears to be low. One autopsy review noted atrial septal aneurysms in approximately 1% of the general population (Silver and Dorsey, 1978), while a recent transesophageal echocardiogram study identified them in 2.2% of healthy volunteers (Agmon et al., 1999).

PFOs with active right-to-left shunts can be identified in situ by transesophageal echocardiography (TEE), transthoracic echocardiography (TTE) or

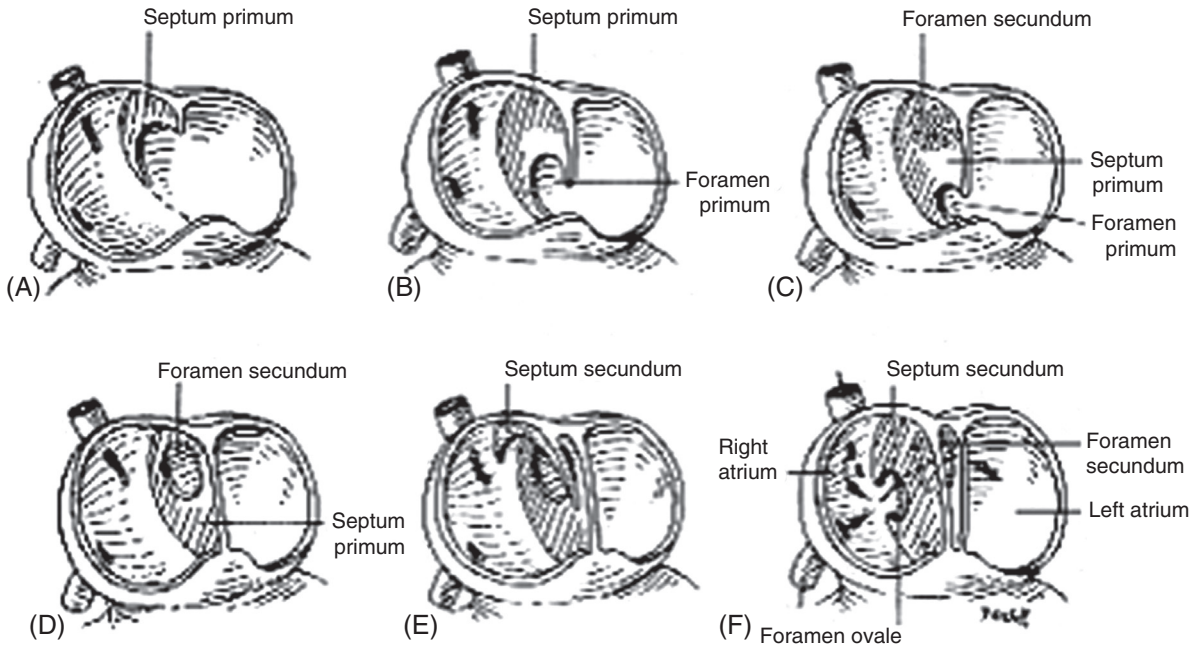

Fig. 36.1. Formation of the atrial septum. Modified with permission from Johnston KE (1988). NMS Human Developmental Anatomy. Lippincott Williams & Wilkins, Baltimore: p. 149. With permission from Lippincott Williams & Wilkins.

transcranial Doppler ultrasound (TCDs). All modalities utilize a "bubble study" in which an aerated solution is injected intravenously and the appearance of air bubbles in the left-sided circulation is monitored; an early appearance of bubbles suggests an underlying PFO. TEE and TTE allow for direct visualization of air bubbles passing from the right atrium to the left atrium, while TCD documents high intensity transients, as these bubbles flow to the middle cerebral arteries. Provoking maneuvers that increase right-sided pressures (e.g., Valsalva) are typically employed to maximize shunting. Lower extremity injection of the aerated solution, while not commonly done, improves PFO detection, as blood returning via the inferior vena cava is preferentially directed towards the interatrial septum by the Eustachian valve (Hamann et al., 1998). Detection of atrial septal aneurysms requires direct visualization and measurement of the dynamic motion of the septum, and thus is possible with TEE and TTE but not TCD.

TEE is the gold standard for detecting PFOs and atrial septal aneurysms. An early study comparing autopsy and TEE detection of PFOs noted a sensitivity of 89% and specificity of 100% (Schneider et al., 1996), though sensitivity is likely even higher now with improved technology. Compared to TEE, TCD has a sensitivity of 91–93% and specificity of 88–100% for PFOs (Jauss et al., 1994; Blersch et al., 2002). The sensitivity of TTE for PFOs, however, may be as low as 47%, largely due to insufficient image resolution (Di Tullio et al., 1992). While no study has directly compared autopsy and TEE findings of atrial septal aneurysms, TEE studies of healthy volunteers have noted a prevalence similar to that seen in previous autopsy reports (approximately 1–2% of the population) (Silver and Dorsey, 1978; Agmon et al., 1999); a similar study with TTE, however, found a prevalence of only 0.22%, suggesting a much lower sensitivity for this modality (Hanley et al., 1985). Overall, a TEE with bubble study remains the preferred cardiac imaging modality in patients with stroke; its retrocardiac viewing angle provides the best images not only of the interatrial septum but also the most common cardio-embolic sources (e.g. left atrial appendage, left-sided heart valves, left ventricle) (Reynolds et al., 2003).

36.3.3. Interatrial septal abnormalities and stroke risk in patients younger than 55 years of age

Despite advances in the identification of disease processes associated with ischemic stroke, the etiology remains elusive in 30–40% of all patients and in 50–60% of patients less than 55 years of age (hereafter referred to as "younger" patients) (Sacco et al., 1989; Cabanes et al., 1993). While different mechanisms may underlie these "cryptogenic" strokes, a growing body of evidence suggests that a significant percentage of unexplained strokes in younger patients are related to abnormalities of the interatrial septum.

Clinically detectable PFOs are present more often in younger patients with ischemic stroke than in age-matched controls; they are also more common in younger patients with cryptogenic stroke than in younger patients with an identifiable source of stroke (e.g., carotid stenosis) (Lechat et al., 1988; Webster et al., 1988; Di Tullio et al., 1992; Cabanes et al., 1993; Mas and Zuber, 1995; Bogousslavsky et al., 1996). Overall, approximately 35–50% of younger patients with cryptogenic ischemic stroke have a PFO, compared to only 4–10% of age-matched patients with stroke attributable to another source. A recent meta-analysis of case-controlled studies found a five-fold increased risk of cryptogenic stroke in younger patients with a PFO (Overell et al., 2000).

Several initial studies suggested that the risk of stroke related to a PFO is strongly influenced by its size. One study reported that patients with PFOs and cryptogenic stroke had significantly larger PFOs than patients with PFO and an identifiable cause of stroke (Homma et al., 2002), while another found larger PFOs in younger patients with cryptogenic stroke than in age-matched healthy controls (Schuchlenz et al., 2000). Similar studies also reported a higher occurrence of resting right-to-left interatrial shunt, as well as a higher frequency of a prominent Eustachian valve (which directs blood towards the foramen ovale), in patients with PFO and cryptogenic stroke (Homma et al., 1994; De Castro et al., 2000).

While these characteristics are likely important, the strongest determinant of stroke risk related to PFO appears to be its association with a coexisting atrial septal aneurysm (Cabanes et al., 1993; Mas and Zuber, 1995; Bogousslavsky et al., 1996). A meta-analysis of several case-control studies showed a 24-fold increased risk of cryptogenic stroke in younger patients with both PFO and atrial septal aneurysms, compared to a five-fold increased risk with PFO alone (Overell et al., 2000). While the exact mechanism underlying the increased risk is unclear, the dynamic motion of the atrial septal aneurysm might strongly influence flow through a PFO; alternatively, an aneurysm could actually be a nidus for thrombus formation and thus a source of emboli. The risk of cryptogenic stroke in patients with atrial septal aneurysms but no PFO has been difficult to estimate, largely due to the very small numbers of such patients thus affected.

It is possible that other coexisting yet unrelated conditions are also important in determining risk of stroke

in younger patients with interatrial septal abnormalities. In particular, any of Virchow's classic risk factors for venous thrombosis (venous stasis, intimal injury, hypercoagulable state) might dramatically affect the risk of an otherwise asymptomatic abnormality. While early studies typically excluded patients with hypercoagulable states, most were done before hypercoagulability attributable to Factor V Leiden, the prothrombin 20210 mutation, or the methylenetetrahydrofolate reductase (MTHFR) polymorphisms was well described. These conditions are now known to constitute an important percentage of inherited risk factors for venous thrombosis. It is thus interesting to note that several recent studies have demonstrated an increased frequency of the prothrombin 20210 mutation in younger patients with PFO and cryptogenic stroke (Karttunen et al., 2003; Lichy et al., 2003; Pezzini et al., 2003). Factor V Leiden was noted to have a significant association in only two of these three studies, while the TT polymorphism of MTHFR was not associated with an increased risk of stroke. Overall, these preliminary data suggest that at least some cryptogenic strokes in young patients might be related to the combination of a PFO with an inherited hypercoagulable state.

Deep vein thrombosis (DVT) is rarely detected in younger patients with PFO and stroke, perhaps because the origin of these venous emboli might be from pelvic rather than lower extremity veins. Autopsy studies of patients with cryptogenic pulmonary or paradoxical emboli have documented isolated pelvic vein thrombus in 16% and 22%, respectively (Johnson, 1951; Corrin, 1964; Modan et al., 1972). A recent study using MR venography in younger patients with ischemic stroke reported a significantly higher incidence of pelvic vein thrombus in patients with cryptogenic stroke compared to patients with an identifiable source of stroke (20% versus 4%); in addition, most patients with pelvic vein thrombus and cryptogenic stroke were also found to have a PFO (Cramer et al., 2004). These data suggest that pelvic vein thrombi might be previously undetected embolic sources in some younger patients with PFOs and cryptogenic stroke.

In summary, data generated during the past two decades have firmly established an association of PFO with cryptogenic ischemic stroke in younger patients. Potential determinants of risk include size, degree of right-to-left shunt at rest, and a Eustachian valve directing flow towards the PFO; the most important risk determinant, however, appears to be the presence of a coexisting atrial septal aneurysm. More recent data have also suggested that an underlying hypercoagulable state might be critical in some patients, though these findings remain preliminary. Overall, these studies provided an important foundation for randomized clinical trials of secondary stroke prevention strategies in this patient population.

36.3.4. Interatrial septal abnormalities and stroke risk in patients 55 years and older

In patients 55 years of age or older (hereafter referred to as "older" patients), interatrial septal abnormalities do not appear to be significantly associated with cryptogenic ischemic stroke. While an early report did suggest a possible connection in this population (Di Tullio et al., 1992), several subsequent studies failed to support this (de Belder et al., 1992; Jones et al., 1994; Zahn et al., 1995). A meta-analysis of case-control studies of older patients with cryptogenic stroke found no risk associated with interatrial septal abnormalities (Overell et al., 2000).

Given the strong association of interatrial septal abnormalities with cryptogenic stroke in younger patients, these observations initially appear quite puzzling. This is particularly true given that PFO size increases with age (Hagen et al., 1984). One possible explanation is that the risk of stroke related to interatrial septal abnormalities in older patients is neutralized by underlying conditions that increase left atrial pressures; this increased pressure might effectively limit or eliminate functional patency of a PFO and reduce mobility of an atrial septal aneurysm into the left atrium, preventing passage of paradoxical emboli. This hypothesis is supported by echocardiography studies that demonstrated that normal aging in healthy adults is associated with decreased left ventricular relaxation and increased left atrial contraction and pressure (Gerstenblith et al., 1977; Thomas et al., 2003).

In addition to normal aging, many disease processes that increase in frequency with age, most notably coronary artery disease and hypertension, can lead to pathologic left ventricular dysfunction and secondarily increased left atrial pressures. Consistent with this hypothesis, one study reported that patients with PFO and an identifiable cause were more likely to have underlying medical conditions associated with increased left atrial pressures than patients with PFO and cryptogenic stroke (Natanzon and Goldman, 2003). Finally, the lack of an interatrial septal abnormality-associated risk in older populations is also likely strongly influenced by the fact that more traditional vascular risk factors become the predominant determinants of stroke in these patients. Taken together, these data may help explain the apparent discrepancy between the risk of stroke related to interatrial septal abnormalities in younger versus older patients.

36.3.5. Secondary prevention of cryptogenic strokes in younger patients with interatrial septal abnormalities

The results of a prospective study on the risk of recurrent stroke in younger patients with or without interatrial septal abnormalities (The Patent Foramen Ovale–Atrial Septal Aneurysm or PFO–ASA trial) were published in December 2001 (Mas et al., 2001). This non-randomized study followed 581 patients, aged 18–55, who had initially presented with a cryptogenic ischemic stroke. Aspirin therapy (300 mg per day) was started in all patients, and the primary end-point was risk of recurrent stroke over a 4-year period.

All patients underwent TTEs and TEEs to evaluate the presence of interatrial septal abnormalities. Overall, 48% were found to have interatrial septal abnormalities—37% with an isolated PFO, 9% with both PFO and atrial septal aneurysm, and 2% with an isolated atrial septal aneurysm. Interestingly, patients without interatrial septal abnormalities were noted to have statistically higher rates of classic vascular risk factors such as hypertension and hyperlipidemia. No significant difference in 4-year recurrent stroke risk was found between those patients without an interatrial septal abnormality (4.2%) and those patients with PFO alone (2.4%). In addition, the degree of shunting across the PFO was not a significant predictor of risk. No recurrence was noted in any of the 10 patients with an atrial septal aneurysm alone. Those patients with both PFO and atrial septal aneurysm, however, had a significantly higher rate of recurrent stroke at 4 years (15.2%).

More recent results from the PFO In Cryptogenic Stroke Study (PICSS) appear to conflict with the findings of the PFO–ASA study (Homma et al., 2002). The PICSS evaluated patients from the Warfarin vs. Aspirin in Recurrent Stroke Study (WARSS) that underwent TEE for evaluation of cardio-embolic sources of stroke. PICSS enrolled 601 patients 30 to 85 years old (average 59±12) who presented with stroke not attributable to a non-interarterial septal abnormality cardio-embolic source. Only 250/601 (42%) of these patients had true cryptogenic stroke, while most had either small-vessel lacunar disease or carotid stenosis. As in many previous studies, PFO was more common in patients with cryptogenic stroke than in patients with an identified source of stroke; also, PFOs in patients with cryptogenic stroke were significantly larger than PFOs in patients with explained stroke. Despite these observations, however, no difference was noted in the 2-year composite end-point of recurrent stroke or death for cryptogenic stroke patients with or without PFOs; in addition, increasing PFO size was not associated with increased risk. Most importantly, in contrast to the findings of the PFO–ASA study, the coexistence of PFO and atrial septal aneurysms was not associated with increased risk of recurrent stroke in this patient population. Finally, no difference was noted between the two treatment arms (aspirin versus warfarin) in cryptogenic stroke patients with or without PFOs.

The apparent discordant findings of the PFO–ASA study and PICCS may be explained by differences in both the study populations and the primary endpoints. The PFO–ASA study focused explicitly on risk of recurrent stroke in younger patients with an initial cryptogenic stroke, while PICSS incorporated a much more heterogeneous patient population and had a composite end-point that included death from any cause. Compared to the PFO–ASA study, patients in PICSS were older (average age 59 versus 43) and had higher rates of chronic medical problems such as hypertension (60% versus 15%) and diabetes (28% versus 4%). Thus, the PFO–ASA study included patients who were generally younger and healthier, a population where interatrial septal abnormalities have been more clearly associated with recurrent stroke.

Currently, the PFO–ASA study provides the best insight into the initial approach to medical management of interatrial septal abnormalities in younger patients with cryptogenic stroke. Antiplatelet therapy likely reduces the risk of recurrent stroke attributable to an isolated PFO or atrial septal aneurysm in these patients, although this is unproven. Those with both PFO and atrial septal aneurysm, however, have unacceptably high rates of recurrence despite aspirin therapy. The best treatment for this population remains to be determined, but options include other antiplatelet agents, anticoagulation with warfarin, or definitive closure of the defect with either surgical or endovascular techniques.

While younger patients with PFO and atrial septal aneurysm might be ideal candidates for surgical or endovascular closure, no randomized controlled trials comparing medical and surgical strategies have been published. Open surgical closure appears to be associated with unacceptably high rates of morbidity and recurrent ischemic events; one study of 91 patients (ages 44.2 ± 12.2) noted a 21% overall morbidity (e.g. atrial fibrillation, tamponade, wound infection) as well as a 17% risk of TIA over 4 years (Dearani et al., 1999).

Percutaneous endovascular techniques of interarterial septal abnormality closure have less morbidity, though long-term effectiveness remains unproven. One case series described outcomes with endovascular closure in 144 patients (ages 50 ± 12) with cryptogenic

cerebral ischemia and interatrial septal abnormalities; only 27% of these patients, however, had PFO and atrial septal aneurysms, with the remainder having PFO alone. Procedural morbidity was low (< 1%) but the percentage of patients with residual shunt was high (21%); recurrent ischemic events were seen in approximately 3% at 1 year, with recurrence correlating with residual shunt (Wahl et al., 2001; Meier and Lock, 2003). A more recent uncontrolled study of endovascular PFO closure in 101 patients with stroke and 144 with TIA noted complete closure in 98%; no recurrent ischemic events were noted in any patient at an average follow-up of 19 months (Onorato et al., 2003). At least three randomized trials of endovascular PFO closure are currently underway, with stroke prevention as the primary endpoint.

Excellent and thorough reviews of these and other observational treatment studies have recently been published (Homma and Sacco, 2005; Kizer and Devereux, 2005). While several approaches show promise, the appropriate treatment for stroke prevention in patients with both PFO and atrial septal aneurysms remains unclear at present, an uncertainty reflected in the recently published American Academy of Neurology Practice Parameter for PFO and atrial septal aneurysm therapy (Messe et al., 2004). The authors conclude that an isolated PFO does not increase the risk of recurrent cryptogenic stroke in patients treated with aspirin, and thus that more aggressive medical or interventional approaches are not justified in these patients. They also note that while younger patients with stroke related to both PFO and atrial septal aneurysms have high recurrence rates despite aspirin therapy, there is unfortunately "insufficient evidence" to guide treatment of younger patients with both PFO and atrial septal aneurysms. For this patient population, many clinicians currently advocate either anticoagulation or endovascular closure. Ongoing trials will hopefully provide better direction in the near future.

36.3.6. Conclusions

Historically, patients younger than 55 years old presenting with unexplained ischemic stroke have provided diagnostic and therapeutic challenges. Several studies demonstrate that interatrial septal abnormalities are risk factors for ischemic stroke in this patient population, and that secondary prevention strategies must be tailored to the nature of the abnormality and associated conditions. An evaluation for the presence of an interatrial septal abnormality, preferably a TEE with bubble study, should be part of the standard workup of stroke in this population. Patients with cryptogenic stroke and documented interatrial septal abnormalities should be evaluated for hypercoagulable states, particularly the prothrombin 20210 mutation and Factor V Leiden; anticoagulation with warfarin is superior to antiplatelet therapy in protecting against DVT and pulmonary emboli in these patients, and may be the best medical treatment in this situation. Finally, recent studies suggest that detecting pelvic vein thrombus further implicates an interatrial septal abnormality as a causative factor; MR venography appears superior to Doppler ultrasound in detecting such thrombi.

Antiplatelet therapy should be the initial treatment for secondary prevention of stroke in younger patients with cryptogenic stroke and an isolated PFO or atrial septal aneurysm, as rates of recurrent stroke while on aspirin therapy are not greater than that seen in patients without interatrial septal abnormalities; PFO size and degree of shunt do not appear to affect recurrent stroke risk associated with an isolated PFO. Antiplatelet therapy for younger patients with both PFO and atrial septal abnormalities, however, may provide only marginal protection; this population may benefit from either anticoagulation or definitive closure of the defect, though neither approach has been studied sufficiently in randomized trials.

In patients older than 55, interatrial septal abnormalities do not appear to be significant risk factors for stroke, perhaps because this population has more common etiologies of stroke and right-to-left atrial shunting is reduced because left atrial pressures are more likely to be elevated. As our understanding of the relationship between interatrial septal abnormalities and stroke in younger patients progresses, however, it will be interesting to see if subpopulations of older patients are identified in which interatrial septal abnormalities have a causative role, such as those with no vascular risk factors, normal left atrial pressures and both PFO and atrial septal aneurysms.

36.4. Valvular disease

36.4.1. Native mitral valve disease

Diseases of the native mitral valve that are associated with cardio-embolic stroke include mitral stenosis, mitral prolapse and mitral annular calcification. Such diseases may lead to cardio-embolic stroke by one of two mechanisms: as an underlying cause of atrial fibrillation (e.g., mitral valve stenosis) or as a presumed substrate for the formation of thrombo-embolic material.

36.4.1.1. Mitral valve stenosis

Stenosis of the mitral valve impedes left ventricular inflow during diastole, and commonly leads to increased left atrial pressures and left atrial enlargement. These

secondary changes are important risk factors for atrial fibrillation (AF), and 30–40% of patients with symptomatic mitral stenosis (MS) develop this arrhythmia (Rowe et al., 1960). Even in the absence of AF, MS remains a risk factor for cardio-embolic disease, presumably by providing a substrate for thrombus formation.

36.4.1.1.1. Etiology

The most common etiology of acquired MS remains rheumatic heart disease. In the USA, the prevalence of this disease and its importance to AF and cardio-embolic stroke continue to decline. The ATRIA study identified the prevalence of AF in a USA patient population of 1.9 million patients to be approximately 1%. Of these, approximately 18,000 patients (only 5%) were noted to have "valvular heart disease." Even if the majority of these valvular lesions were MS related to rheumatic heart disease, their overall prevalence in the general AF population remains quite low, suggesting that the vast majority of AF cases in the USA are not related to MS (Go et al., 2001). In developing countries, however, rheumatic heart disease-related MS remains one of the most important causes of cardio-embolic stroke. One recent report suggests that up to 50–60% AF cases in India are associated with rheumatic heart disease (Vora, 2006).

36.4.1.1.2. MS with atrial fibrillation

While never studied in randomized trials, it is widely accepted that patients with AF related to MS carry a high risk of cardio-embolic stroke (equivalent to or perhaps even greater than high-risk patients with non-valvular AF), and that anticoagulation therapy is the optimal choice to best mitigate this risk. Observational studies suggest that the 5–10% annual risk of cardio-embolism in this population can be reduced four- to fifteen-fold with systemic anticoagulation (Abernathy and Willis, 1973). These observations are also supported by the wealth of data from randomized trials of non-valvular AF that demonstrated the benefit of anticoagulation over either antiplatelet therapy or no therapy.

The 2004 ACCP and the 2006 American Heart Association (AHA) guidelines both recommend anticoagulation with a target INR of 2.5 (range 2.0–3.0) for all patients with rheumatic MS and AF (persistent or paroxysmal). (In the terminology of guidelines for NVAF, all valvular AF patients should be considered "high-risk" patients.) For those with cardio-embolism despite adequate anticoagulation, the ACCP guidelines suggest the addition of low-dose aspirin (75–100 mg/day); if unable to tolerate aspirin, dipyridamole (400 mg/day) or clopidogrel is recommended.

36.4.1.1.3. MS with sinus rhythm

The risk of cardio-embolism attributable to MS in the absence of associated AF is considerably lower, but nonetheless significant. Current data suggest that prior systemic embolism, documented left atrial thrombus, age, and left atrial size are important factors that influence this risk (Bonow et al., 2006). Most guidelines, including the 2004 ACCP and the 2006 AHA algorithms, recommend indefinite anticoagulation with a target INR of 2.5 (range 2.0–3.0) for patients with rheumatic MS, in sinus rhythm, and a history of systemic embolism.

The utility of echocardiography to guide anticoagulation of patients with asymptomatic MS in sinus rhythm remains controversial. Recent guidelines by the ACCP and AHA strongly advocate anticoagulation for patients with asymptomatic MS in sinus rhythm with documented left atrial thrombus; these guidelines also recommend consideration of anticoagulation in patients with either spontaneous echo contrast or a left atrial diameter of 55 mm or more. The utility of surveillance echocardiography in asymptomatic patients, however, remains unproven, and little data is available to direct the frequency of such studies.

36.4.1.1.4. Valvuloplasty for MS

Patients undergoing balloon valvuloplasty for MS for cardiac indications are likely to be at high risk for thrombo-embolic events in the periprocedural period. The ACCP guidelines recommend anticoagulation with a target INR of 2.5 for 3 weeks prior to and 4 weeks following this procedure. As with elective conversion of new-onset AF, it is possible that transesophageal echocardiography could identify patients at low-risk for cardio-embolic complications (e.g., no thrombus identified) and negate the need for periprocedural anticoagulation, though this remains unstudied.

36.4.1.2. Mitral annular calcification

Mitral annular calcification (MAC) is a chronic degenerative process characterized by calcification and fibrosis of the mitral valve support ring. It is most commonly seen in elderly women, with an increased prevalence in patients with chronic renal failure, secondary hyperparathyroidism, aortic stenosis, coronary artery disease, and hypertension. Cardiac complications of severe MAC can include mitral valve stenosis or regurgitation, infective endocarditis, left atrial enlargement, atrial fibrillation, and heart block. Many of these complications are established risk factors for cardio-embolism and have specific proven therapies for reduction of stroke risk (i.e., atrial fibrillation, mitral stenosis, infective endocarditis).

Multiple studies have also shown that MAC is itself a strong independent risk factor for stroke. The Framingham Heart Study identified a two-fold increase risk of stroke in patients with MAC compared to those without MAC, even after adjusting for traditional vascular risk factors (Fox et al., 2003). These observations were supported by the recently published Strong Heart Study, an evaluation of MAC-associated stroke risk in Native American patients without other cardiovascular disease, which noted an approximate three-fold increase in stroke risk attributable to MAC (Kizer et al., 2005).

MAC likely directly predisposes to cardio-embolism by one of two mechanisms: as a substrate for formation of fibrin-rich thrombus or by fragmentation and embolization of ulcerated calcified debris from the annular ring itself. It remains unclear which mechanism is most common in these patients, as echocardiography studies have identified both calcified and non-calcified MAC-associated mobile elements (Eicher et al., 1997; Shohat-Zabarski et al., 2001), and autopsy studies have reported both calcified and non-calcified emboli in the cerebral vessels in this patient population (Burnside and Desanctis, 1972; Lin et al., 1987).

No data are available to direct antithrombotic therapy in patients with MAC and no history of systemic embolism. Most guidelines recommend chronic anticoagulation (target INR 2.5, range 2.0–3.0) for patients with cardio-embolism and isolated MAC, unless the embolus is proven to be calcific in nature. For patients with documented calcified emboli or those with repeated thrombo-embolism despite anticoagulation, valve replacement may be the best treatment option.

36.4.1.3. Mitral valve prolapse

Mitral valve prolapse (MVP) is a myxomatous degeneration of one or both mitral valve leaflets, leading to redundancy and bulging or "prolapse" of the leaflet into the left atrial chamber during ventricular systole (reviewed by Hayek et al., 2005). Studies from the 1980s suggested that MVP was quite common, particularly in young women, with one study detecting MVP in 38% of teenage girls surveyed (Warth et al., 1985). In addition, early case-controlled studies found that MVP was more common in patients with unexplained ischemic stroke (Barnett et al., 1980; Sandok and Giuliani, 1982). These observations suggested that MVP, perhaps by providing a substrate for thrombus formation, might be an important cause of cryptogenic cardio-embolic stroke in young patients.

Advances in echocardiography and an improved understanding of the normal dynamic anatomy of the mitral valve, however, have led to a more precise definition of MVP (single or bileaflet prolapse of at least 2 mm beyond the long-axis annular plane) and a re-evaluation of its putative role in ischemic stroke. Using these criteria, the prevalence of MVP is estimated to be 2–3%, with similar rates in both men and women (Bonow et al., 2006). Several recent studies have demonstrated that MVP diagnosed by these criteria does not appear to be associated with ischemic stroke in patients younger than 45–50 years of age (Freed et al., 1999; Gilon et al., 1999; Avierinos et al., 2003). One of these reports, an Olmsted County community-based study, did find an association of MVP with ischemic stroke in patients older than 50 (Avierinos et al., 2003). For these older patients with MVP, the annual risk of a cerebral ischemic event was 0.7%, twice that of the control population without MVP. Predictors of ischemia included advancing age, MV leaflet thickening, detection of atrial fibrillation on follow-up evaluation, and subsequent need for valvular surgery. Overall, the risk of stroke was most strongly tied to the development of mitral regurgitation and its associated problems (e.g., atrial fibrillation), leading the authors of this study to conclude that MVP has only an "indirect role" in ischemic events.

Given the absence of strong evidence linking MVP to ischemic stroke in the general population, most guidelines suggest against the routine use of antithrombotic therapy in patients with asymptomatic MVP (that is, no history of systemic embolism, cerebral ischemia, or atrial fibrillation). Some authors advocate antiplatelet therapy for asymptomatic patients with "high-risk" imaging features (e.g., thickened valve leaflets), but the utility of serial imaging studies and empiric therapy remain unstudied. For asymptomatic patients with atrial fibrillation, MVP is not itself a "high-risk factor," and the choice of antithrombotic therapy can be made according to standard algorithms noted above.

Most guidelines recommend indefinite aspirin therapy for patients with unexplained cerebral ischemia who are found to have isolated MVP. (Note that this recommendation would be the same whether or not MVP was identified.) Recent guidelines from the American Heart Association also suggest that anticoagulation with warfarin be considered in this situation if there is echocardiographic evidence of redundancy or thickening of the mitral valve leaflets or if significant mitral regurgitation is present. The latter observation should raise suspicion for the presence of paroxysmal atrial fibrillation as the underlying cause of stroke. Finally, the appropriate therapy for patients with isolated MVP and recurrent cerebral ischemia despite aspirin therapy remains unclear, though most guidelines advocate anticoagulation with warfarin (target INR 2.5, range 2.0–3.0) in this setting.

36.4.2. Native aortic valve disease

Aortic sclerosis (degenerative thickening and calcification of the valve, with or without associated stenosis) was initially identified as a potential cardio-embolic stroke, particularly given early autopsy evidence of calcific systemic microemboli in such patients. While aortic sclerosis is associated with an increased risk of cardiovascular complications (e.g., myocardial infarction), several studies have failed to find a relationship to cardio-embolic ischemic stroke (Boon et al., 1996; Kizer et al., 2005). In addition, there is currently no strong data to suggest an association of either aortic stenosis or aortic regurgitation with cardio-embolic stroke. Given these observations, most guidelines recommend against the use of anticoagulation for either the primary or secondary prevention of ischemic stroke in patients with native aortic valve disease.

36.4.3. Papillary fibroelastoma of the mitral and aortic valves

Papillary fibroelastomas are extremely rare and benign tumors that most commonly arise from the valvular endocardium. They are the third most common primary cardiac tumor, and the most common cardiac valvular tumor. A 2003 review of all 725 cases identifiable by a literature search noted aortic valve involvement in 36% of cases and mitral valve involvement in 30% (Gowda et al., 2003). While uncommon, these benign growths have been associated with systemic embolism, including ischemic stroke (Sastre-Garriga et al., 2000; Gowda et al., 2003). Fortunately, the routine use of echocardiography in the evaluation of patients with embolic stroke allows for fairly straightforward detection as mobile masses on either the valve surface or its associated chordae. Limited data are available to guide antithrombotic therapy for such lesions; most guidelines appear to favor surgical excision (Borsani et al., 2006).

36.4.4. Prosthetic mitral and aortic valves

One of the most feared complications of cardiac valve replacement is cardio-embolic stroke. The risk of thrombo-embolism related to prosthetic cardiac valves is determined by multiple factors, including valve location (mitral versus aortic), the specific type of valve employed (mechanical versus bioprosthetic) and the presence of co-morbid conditions (e.g., atrial fibrillation, left ventricular dysfunction). It is uniformly accepted that targeted antithrombotic therapy is critical for minimizing this risk. As treatment guidelines are well established, with recently published exhaustive reviews by the American College of Chest Physicians (Salem et al., 2004) and the American College of Cardiology/American Heart Association (Bonow et al., 2006), this section will simply highlight the importance of general risk factors without reviewing the large literature pertaining to each specific type of valve and location. A summary of current antithrombotic guidelines for specific prosthetic valves, according to location, is provided in Table 36.3.

36.4.4.1. Valve location

Regardless of the type of valve used, the risk of cardio-embolism is greater for prosthetic valves in the mitral position compared to the aortic position. This risk is presumably related to the relatively lower flow velocities and pressure across the valve, increased left atrial size, enhanced potential for stasis of left atrial blood flow, and a predisposition to paroxysmal atrial fibrillation. As a general rule, prosthetic valves in the mitral position require more aggressive antithrombotic therapy (e.g., higher INR targets) than prosthetic aortic valves.

36.4.4.2. Type of valve

A primary benefit of mechanical valves is their durability, with a relatively low risk of deterioration over time necessitating replacement. Unfortunately, mechanical valves have an extraordinarily high risk of thrombo-embolism in the absence of anticoagulation therapy: in one study, the rates of embolism or valve thrombosis for St. Jude bileaflet valves in the mitral and aortic position were 22% per year and 12% per year, respectively (Baudet et al., 1995). Tilting disk and caged mechanism valves likely have even higher thrombo-embolic potential. Multiple studies have demonstrated that anticoagulation clearly decreases this risk, although the frequency of cardio-embolism nonetheless remains significant (for the St. Jude bileaflet valves, for example, anticoagulation can lower the annual rate of thrombo-embolism to 2–5%), and potential bleeding complications must be considered. Importantly, the risk of mechanical valve thrombo-embolism does not appear to abate with time, and aggressive anticoagulation therapy must be used on lifelong basis. The recommended target INR range is heavily influenced by the specific mechanism of the valve (e.g. bileaflet, tilting disk, caged).

Bioprosthetic cardiac valves were created in large part to decrease thrombogenic potential and the need for lifetime anticoagulation. Endothelialization of the bioprosthetic valve occurs over the course of several months, and many guidelines suggest that such prostheses can be treated as a native valve 3 months

after implantation (Bonow et al., 2006). The risk of thrombo-embolism from a bioprosthetic valve in the initial 3 months, however, appears similar to mechanical valves, particularly for those in the mitral position (Heras et al., 1995). This risk appears to be especially high in the first 2–3 days following insertion in either location.

An early observational study of bioprosthetic valves in the mitral position noted a 3-month risk of stroke of 5.9% in patients (4 out of 68) not receiving anticoagulation, compared to 0% (0 out of 182) receiving anticoagulation (Ionescu et al., 1982). For bioprosthetic valves in the aortic position, the risk appears to be lower and aspirin therapy is likely as protective as anticoagulation. A non-randomized observational study reported that the 3-month risk of stroke in such patients treated with either low-molecular weight heparin and warfarin (INR goal 2.0–3.0) or aspirin was similar (2.1% in the aspirin group, 4.6% in the warfarin group; not significantly different), with no difference noted in bleeding complications (Gherli et al., 2004). After 3 months, the risk of thrombo-embolism from bioprosthetic valves in either the mitral or aortic position decreases dramatically, and aspirin therapy appears to be sufficient in most cases. Many observational studies suggest that patients on long-term aspirin therapy have an annual risk of thrombo-embolism of less than 1% overall (perhaps below 0.2% per year for patients with a bioprosthetic valve in the aortic position) (Goldsmith et al., 1998).

In summary, mechanical valves provide greater long-term durability, but carry a persistently elevated thrombogenic potential that necessitates life-long anticoagulation. Bioprosthetic valves offer the potential for limited use of anticoagulation (within the first few months) followed by long-term antiplatelet therapy. Bioprosthetic valves, however, are much less durable and frequently require replacement; for this reason, many centers do not use bioprosthetic valves in patients younger than 60, though the continued evolution of bioprosthetic valves will likely lead to their more common use in younger patient populations.

36.4.4.3. Associated risk factors

The thrombo-embolic risk in patients with prosthetic valves is strongly influenced by co-morbid conditions, including atrial fibrillation, previous thrombo-embolism, left ventricular dysfunction, hypercoagulable states, left atrial enlargement, and myocardial infarction. The presence of any of these conditions is significant enough that most guidelines recommend a very aggressive antithrombotic regimen (a relatively high INR range (2.5–3.5) with the addition of an antiplatelet agent).

36.4.4.4. Principles of antithrombotic therapy for prosthetic valves

36.4.4.4.1. Mechanical valves

(Table 36.3) As a general rule, all patients with mechanical valves require anticoagulation, with the goal INR determined by the specific type of valve, its location and associated risk factors (reviewed by Bonow et al., 2006). Mechanical valves in the mitral position carry the greatest thrombogenic potential of any prosthetic valve, and most studies suggest that anticoagulation with a relatively high INR target (goal 3.0, range 2.5–3.5) provides the best risk-to-benefit profile in this population. Thrombo-embolic risk for mechanical valves in the aortic position is highly dependent upon the specific valve mechanism, with the highest risk seen in “caged ball” or “caged disk” valves (fortunately, these valves are now only rarely encountered). Of the commonly used mechanical aortic valves, tilting disk valves have greater thrombo-embolic risk than bileaflet valves. These observations, combined with the results of multiple observational reports of warfarin anticoagulation (studied over a wide range of target INRs), are the basis of the following treatment recommendations for aortic mechanical valves: (1) bileaflet valve, target INR 2.5 (range 2.0–3.0); (2) tilting disk valve, target INR 3.0 (range 2.5–3.5); and (3) caged mechanism valve, target INR 3.0 (range 2.5–3.5) with the addition of daily aspirin. Finally, the presence of any high-risk factor (atrial fibrillation, myocardial infarction, left ventricular dysfunction, left atrial enlargement, prior thrombo-embolism, or underlying hypercoagulability) in a patient with any type of mechanical valve (whether mitral or aortic) greatly elevates the thrombo-embolic risk, and most guidelines recommend aggressive antithrombotic therapy: anticoagulation with a target INR of 3.0 (range 2.5–3.5) combined with aspirin (75–100 mg/day).

36.4.4.4.2. Bioprosthetic valves

Absent associated risk factors such as atrial fibrillation, the chronic risk of thrombo-embolism from a bioprosthetic mitral or aortic valve appears to be quite low. Many studies suggest that indefinite aspirin therapy is sufficient for minimizing this risk. In the initial 3 months following insertion, however, the potential for thrombo-embolism appears to be significant. Anticoagulation for 3 months following insertion of a bioprosthetic valve in the mitral position is strongly recommended; for the initial 3 months following placement of a bioprosthetic valve in the aortic position, it appears reasonable to use either anticoagulation or aspirin therapy. For patients with bioprosthetic valves

Table 36.3

Summary of the 2004 American College of Chest Physician Antithrombotic Guidelines for Prosthetic Heart Valves

Mechanical valves			
Location	Type of valve	Risk factors*	Antithrombotic therapy
Mitral	Any	No	Warfarin, INR 3.0 (2.5–3.5)
Aortic	Bileaflet	No	Warfarin, INR 2.5 (2.0–3.0)
	Tilting disk	No	Warfarin, INR 3.0 (2.5–3.5)
	Caged mechanism	No	Warfarin, INR 3.0 (2.5–3.5) + aspirin**
Any	Any	Yes	Warfarin, INR 3.0 (2.5–3.5) + aspirin**
Bioprosthetic valves			
Location	Time window	Risk factors*	Recommended antithrombotic therapy
Mitral	Initial 3 months	No	Warfarin, INR 2.5 (2.0–3.0)
	After 3 months	No	Aspirin (75–325 mg/day)
Aortic	Initial 3 months	No	Either warfarin (target INR 2.5) or aspirin
Any	Any	Yes	Warfarin, INR 2.5 (2.0–3.0)

*High-risk factors: atrial fibrillation, myocardial infarction, left ventricular dysfunction, left atrial enlargement, prior thromboembolism, or hypercoagulability.
**Aspirin (75–100 mg/day).

and an associated high-risk factor (see above), indefinite anticoagulation is recommended. Whether aspirin therapy should be combined with anticoagulation for this patient population is controversial, being advocated by some guidelines but not others.

36.4.4.5. Anticoagulation combined with antiplatelet agents

A recent Cochrane meta-analysis evaluated 11 prospective randomized controlled trials comparing anticoagulation monotherapy to anticoagulation combined with antiplatelet agents (six trials with dipyradimole, five trials with aspirin) in over 2,400 patients with prosthetic valves (Little and Massel, 2003). Combination therapy was associated with a statistically significant reduction in both thrombo-embolic events (odds ratio 0.39, $p < 0.00001$) and total mortality (odds ratio 0.55, $p = 0.0003$), with aspirin and dipyridamole providing similar benefit. Combination therapy was associated with an increased risk of major bleeding (odds ratio 1.66, $p = 0.003$); the reviewers concluded that this risk was "acceptable" given the overall significant benefits noted. Many of these studies, however, utilized high-dose antiplatelet agents along with INR ranges that are no longer routinely recommended (e.g. 3.0–4.5). Limited studies of low-dose aspirin (e.g. 100 mg/day) combined with anticoagulation targeting an INR between 2.0 and 3.5 suggest that aspirin can decrease the frequency not only of thrombo-embolic events but also of overall cardiovascular mortality, with only a small increase in the risk of hemorrhagic complications (Cappelleri et al., 1995).

Whether aspirin therapy should be routinely combined with anticoagulation for patients with prosthetic heart valves remains controversial, being advocated by some but not all guidelines. While the 2006 ACC/AHA guidelines (Bonow et al., 2006) recommend combination therapy (adjusted-dose warfarin with 75–100 mg/day aspirin) for all patients with a mechanical valve (regardless of type, location, or associated comorbid conditions) and for all patients with a bioprosthetic valve and an associated high-risk factor, the 2004 ACCP guidelines (Salem et al., 2004) recommend combination therapy only in patients with mechanical valves who have an associated high-risk factor.

36.4.5. Infective endocarditis of native and prosthetic valves

Prior to the routine use of antimicrobial therapy for infective endocarditis (IE), the incidence of systemic embolism was greater than 70%, with over half involving the cerebral circulation (Baddour et al., 2005). In the modern era, systemic embolism remains the presenting clinical event in 15–40% of patients with IE, and occurs in 5–20% of IE patients despite the institution of therapy (Vilacosta et al., 2002; Anderson et al., 2003; Thuny et al., 2005; Fabri et al., 2006). Key features that likely modulate the risk of systemic embolism include the use of antimicrobial agents, the type of valve (prosthetic versus native) and its location (aortic versus mitral), echocardiography findings and the underlying infectious organism. Whether or not antithrombotic therapy is indicated in IE remains controversial, in part because much of the relevant literature is based upon observations made prior to the development of highly sensitive and specific clinical and radiographic diagnostic criteria for IE. Given these recent advancements, it is likely that our appreciation

of the risks and benefits of antithrombotic therapy in IE will rapidly evolve in the coming years.

The single most important intervention for decreasing IE-related embolism is the prompt use of antimicrobial agents. Such therapy decreases the risk of embolism by at least four-fold within the first week of therapy alone (Paschalis et al., 1990), with further dramatic reduction following 2 full weeks of treatment. In one study, the rate of systemic emboli during the initial week of antimicrobial therapy was 13 per 1,000 patient-days, compared to a rate of 1.2 per 1,000 patient-days following completion of the second treatment week (Steckelberg et al., 1991). Finally, several studies have suggested that 65–80% of embolic events occur within the first 2 weeks of treatment, suggesting a low overall long-term risk once the patient has received antimicrobial treatment through this acute period (Steckelberg et al., 1991; Vilacosta et al., 2002; Fabri et al., 2006).

36.4.5.1. Valve location and type

As with valvular disease in general, the risk of systemic embolism related to IE appears to be greater for mitral disease compared to aortic disease (Cabell et al., 2001; Anderson et al., 2003; Baddour et al., 2005), though not all studies found this association (Di Salvo et al., 2001; Thuny et al., 2005). In addition, while early observational studies led to the widespread acceptance that prosthetic valve IE carries a much greater risk of systemic embolism than native valve IE, multiple recent reports have suggested that these risks are similar (Cabell et al., 2001; Di Salvo et al., 2001; Vilacosta et al., 2002; Deprele et al., 2004). Interpreting these studies is difficult, however, as most patients with prosthetic valve IE are anticoagulated at the time of diagnosis and then subsequently maintained on this treatment (in the absence of stroke), whereas most patients with native valve IE are not routinely treated with this therapy (see later in this chapter). Many studies have not adjusted for this treatment difference, making direct comparisons difficult. Overall, the weight of the current literature suggests that prosthetic valve IE is associated with greater risk of embolism than native valve IE.

36.4.5.2. Echocardiography findings

Multiple studies have investigated the utility of echocardiography for the identification of high-risk patients with IE. Many early studies, particularly those that utilized transthoracic echocardiography, produced conflicting results. More recent investigations of transesophageal echocardiography (TEE) in IE have generally shown that two echocardiographic features are associated with a high risk of embolism despite antimicrobial therapy: the presence of vegetations greater than 10 mm in size and the presence of mobile vegetations (Vilacosta et al., 2002; Deprele et al., 2004; Thuny et al., 2005). It remains controversial, however, whether such observations should lead to more aggressive intervention (e.g. antithrombotic therapies or surgical repair).

36.4.5.3. Infectious organisms

The risk of systemic embolism in IE is also heavily influenced by the causative infectious agent. Several studies have noted a two- to four-fold increased risk of embolic events in *Staphylococcus aureus* and *Streptococcus bovis* IE (Thuny et al., 2005; Fabri et al., 2006). Atypical causes of IE, including the HACEK organisms and Candida, also appear to carry higher risk of systemic embolism.

36.4.5.4. Antithrombotic therapy

As noted above, anticoagulation therapy for either native or prosthetic valve IE remains very controversial, and recommendations are based largely upon uncontrolled observational studies. Such studies from the 1940s to 1980s suggested that anticoagulation for native valve IE did not reduce embolism rates but did increase the frequency of hemorrhagic complications, particularly intracranial hemorrhage (reviewed by Baddour et al., 2005). Given these observations, most current guidelines consider the use of anticoagulation contraindicated in patients with native valve IE (with or without a history of systemic embolism). Prosthetic mechanical valve IE is a particularly difficult situation, as most patients are on chronic anticoagulation at the time of diagnosis, and the long-term risk of thrombo-embolism is clearly higher in prosthetic valves compared to native valves. While not rigorously studied in controlled trials, anticoagulation therapy is commonly continued in mechanical valve IE patients who have no history of cerebral embolism, largely given the concern of abruptly stopping anticoagulation in this population. This concern, however, must be tempered by early reports of increased risk of intracranial hemorrhage in patients with mechanical valve IE on anticoagulation therapy (Lieberman et al., 1978; Wilson et al., 1978). In particular, the report of a dramatic increase in mortality related to cerebral embolism and hemorrhage in *Staphylococcus aureus* prosthetic valve IE (Tornos et al., 1999) led to a 2006 AHA recommendation that anticoagulation be held for at least the first 2 weeks of antibiotic therapy in this specific patient population (Baddour et al., 2005).

The potential role for antiplatelet agents in acute IE was recently studied in a multicenter, double-blinded, placebo-controlled randomized trial. One-hundred fifteen patients with left-sided IE (91 with native valve

disease, 24 with prosthetic valve disease) and no history of stroke were randomized to either placebo or aspirin (325 mg/day) therapy (Chan et al., 2003). Importantly, anticoagulation therapy was continued in all patients with prosthetic valve IE. Overall, aspirin had no effect on the size of vegetations on follow-up imaging, and no impact on the rate of systemic embolism. While not significant, a trend towards increased hemorrhagic complications was noted in the aspirin group (a trend that was similar in both the native and prosthetic valve IE populations). These data support the conclusion that aspirin therapy is not beneficial in either native or prosthetic valve IE.

In summary, current guidelines recommend against the use of either anticoagulation or antiplatelet therapy in patients with native valve IE (whether or not there is a history of cerebral embolism); in this scenario, antimicrobial therapy is unquestionably the most important treatment. For patients with prosthetic valve IE, anticoagulation is commonly continued; intravenous unfractionated heparin is typically used, allowing for rapid reversal with clinical deterioration or the need for surgical repair of the valve. This practice, however, is controversial, and receives only a weak endorsement in the 2004 ACCP and 2006 AHA guidelines. The addition of aspirin to anticoagulation is not recommended. Anticoagulation should likely be terminated in patients with *Staphylococcus aureus* prosthetic valve IE, at least for the first 1–2 weeks of antibiotic therapy. Finally, ongoing studies that incorporate current clinical and echocardiographic criteria for the diagnosis of IE may ultimately help stratify which patients with prosthetic valve IE might benefit from anticoagulation or other therapies (e.g., early surgery).

36.4.6. Nonbacterial thrombotic endocarditis

Nonbacterial thrombotic endocarditis (NBTE), also known as "cachetic" or "marantic" endocarditis, refers to a syndrome in which fibrin-rich, sterile vegetations form on cardiac valves (reviewed by Lopez et al., 1987). NBTE is classically seen in patients with an underlying malignancy or chronic debilitating disease, but is also associated with acute coagulopathic states such as disseminated intravascular coagulation—the unifying feature of these diseases is hypercoagulability. Prior to the routine use of transesophageal echocardiography (TEE), the diagnosis of NBTE was most commonly made at autopsy. Currently, the diagnosis is largely based upon the detection of valvular vegetations, usually by TEE, in the context of negative blood cultures. Its diagnosis nonetheless remains elusive in many cases, as clinical features seen in infective endocarditis (e.g., heart murmur) are frequently absent, and residual vegetations following a symptomatic thrombo-embolic event are often small and difficult to detect by even TEE (reviewed by Salem et al., 2004). NBTE should be suspected in any patient with a known malignancy or coagulopathy who presents with an unexplained large vessel embolic stroke; likewise, the diagnosis of cryptogenic NBTE should prompt a search for an occult malignancy.

The most important therapy for NBTE is treatment of the underlying disease process (e.g., malignancy). While not rigorously studied, acute treatment with intravenous unfractionated heparin likely decreases thrombo-embolic events; interestingly, anticoagulation with vitamin K antagonists does not appear to provide a similar benefit (Sack et al., 1977; Lopez et al., 1987; Rogers et al., 1987). The current ACCP guidelines recommend the use of intravenous or subcutaneous heparin for patients with NBTE and systemic embolism, with the latter being employed for chronic outpatient management.

36.4.7. Libman–Sacks endocarditis

Libman–Sacks endocarditis is a unique type of valvular disease that is seen most commonly in systemic lupus erythematosus and antiphospholipid syndrome, with the highest incidence seen in patients with both underlying disease processes (Hojnik et al., 1996). These aseptic vegetations, which form secondary to the deposition of complement and immunoglobulin, provide a substrate for thrombus formation and subsequent embolism. Patients found to have unexplained NBTE (aseptic vegetations) during a workup for embolic stroke should thus be screened not only for underlying malignancy but also for potential connective tissue disease and antiphospholipid syndrome.

Secondary stroke prevention in patients with Libman–Sacks endocarditis (without associated antiphospholipid syndrome), while not thoroughly studied, typically involves anticoagulation (with target INR range of 2.0–3.0) combined with immunomodulatory therapy for any underlying connective tissue disease. While high-intensity anticoagulation (INR range 3.0–4.0) was long believed to be required for secondary prevention of thrombosis in patients with antiphospholipid syndrome, recent studies have suggested that more moderate intensity (INR range 2.0–3.0) provides similar protection (Crowther et al., 2003).

36.5. Left ventricular disease

Two common left ventricular diseases are associated with an elevated risk of cardio-embolic stroke: recent myocardial infarction and congestive heart failure.

The role of antithrombotic therapies for primary and secondary stroke prevention has been fairly well studied in patients with recent myocardial infarction (though mostly as a "secondary outcome" in many trials designed to primarily assess cardiovascular disease). These trials have been exhaustively reviewed in recent guideline statements from the American College of Cardiology/American Heart Association (ACC/AHA) (Antman et al., 2004) and the American College of Chest Physicians (ACCP) (Harrington et al., 2004), and will be summarized below. Less data is available to guide antithrombotic therapy of patients with severely depressed left ventricular function, though recent and ongoing clinical trials will likely provide such guidance in the near future.

36.5.1. Acute myocardial infarction (AMI)

Acute myocardial infarction predisposes patients to subsequent cardioembolic stroke, presumably from thrombus formation along a hypokinetic or akinetic section of the infarcted ventricular wall. While much of the extensive literature on antithrombotic therapy in post-AMI patients has focused on prevention of recurrent MI (sometimes with ischemic stroke studied as a secondary outcome), many recent trials have incorporated ischemic stroke into composite primary outcomes. Given that the benefit of antiplatelet therapy is well established in this patient population, both for cardiovascular and cerebrovascular disease, a primary question is whether anticoagulation, with or without aspirin, might provide greater protection in this patient population. This section will thus focus largely upon several recently conducted randomized controlled trials that addressed this specific issue.

It is well accepted that antiplatelet therapy in post-MI patients reduces both subsequent ischemic stroke and recurrent MI. The Antiplatelet Trialist's collaboration analysis of over 19,000 patients enrolled in AMI antiplatelet trials found a small but significant decrease in the short-term risk of ischemic stroke (mean treatment duration of 1 month following AMI), from 0.6% in the control arm to 0.3% in the antiplatelet arm (Anonymous, 2002). Overall, antiplatelet therapy resulted in two fewer strokes per 1,000 patients. An even greater benefit from antiplatelet therapy was seen in the reduction of vascular death and recurrent MI. Finally, the indication for antiplatelet therapy following AMI has been bolstered by the success of percutaneous coronary intervention, particularly the use of coronary stents. Dual antiplatelet therapy (aspirin and clopidogrel) is commonly used in the acute period following stenting, with subsequent lifelong monotherapy, usually with aspirin.

The potential benefit of anticoagulation, with or without aspirin, over aspirin alone for the prevention of death, ischemic stroke, or recurrent myocardial infarction following AMI has now been studied in several large, randomized controlled trials. Two trials have investigated the combination of low, fixed-dose anticoagulation (achieving INR < 2.0) with aspirin versus aspirin alone in acute MI patients, each with a composite primary outcome of cardiovascular death, recurrent MI or ischemic stroke. The Coumadin Aspirin Reinfarction Study (CARS) randomized 8,803 patients and had a median follow-up of 14 months (Anonymous, 1997b), while the LoWASA trial randomized 3,300 patients and had a median follow-up of 5 years (Herlitz et al., 2004). In neither study did the combination therapy arm decrease the rate of composite primary outcome. In the LoWASA trial, the secondary endpoint of ischemic stroke was reduced by combination therapy, though this finding was not supported by the CARS trial.

The use of adjusted-dose warfarin (target INR > 2), with or without aspirin, in patients with AMI has been recently evaluated in several trials. Of these, the WARIS II trial (Hurlen et al., 2002) likely provides the best insight, given its large enrollment (3,630 patients) and long duration of follow-up (mean 4 years). In this trial, patients less than 75 years of age with acute ST-segment elevation MI were randomized to aspirin monotherapy (160 mg daily), warfarin monotherapy (adjusted-dose, target INR 2.8–4.2) or combination therapy (adjusted-dose warfarin, target INR 2.0–2.5, with aspirin 75 mg daily). The primary endpoint, a composite of cardiovascular death, stroke, or recurrent MI, was noted in 20% of the aspirin monotherapy arm; this rate was significantly lower in both the combination therapy arm (15%, $p = 0.001$ versus aspirin) and the warfarin monotherapy arm (16.7%, $p = 0.03$ versus aspirin). Major bleeding episodes were statistically more common in the warfarin arms, though nonetheless remained uncommon (combination therapy, warfarin monotherapy, and aspirin monotherapy rates of 0.57%, 0.68%, and 0.17%, respectively, over a mean of 4 years).

Both the 2006 ACC/AHA and 2004 ACCP guidelines for antithrombotic therapy following AMI stress that the WARIS II and similar trials reported significant problems with implementing warfarin therapy; despite close monitoring, less than half of patients were routinely found to be within the target INR range, and a significant number of patients ultimately discontinued therapy altogether. These observations, combined with the small but significant increase in serious bleeding and the fact that only patients less than 75 years of age were studied, have tempered enthusiasm for the routine use of anticoagulation in this population. In general, both the ACC/AHA and ACCP guidelines advocate that

most patients with AMI, including all who receive acute coronary stenting, be treated with antiplatelet agents alone. For patients with a clear indication for anticoagulation (including atrial fibrillation, left ventricular thrombus, post-MI cerebral embolism, or extensive regional wall-motion abnormality), most guidelines suggest either high-intensity warfarin monotherapy (adjusted-dose, target INR 2.5–3.5) or combination therapy with adjusted-dose warfarin (target INR 2.0–3.0) and low-dose aspirin (75–162 mg/day).

36.5.2. Congestive heart failure

A relationship between depressed left ventricular function and ischemic stroke risk has been noted in several recent studies. The SAVE trial (Survival and Ventricular Enlargement) evaluated over 2,000 patients with AMI and an ejection fraction (EF) below 40%, reporting an estimated 5-year rate of stroke of 8.1% (1.5% per year) (Loh et al., 1997). Each 5% decrease in EF was associated with an 18% increase in the risk of stroke. The absence of antithrombotic therapy was an independent risk factor for stroke; treatment with anticoagulation was associated with an 81% reduction in the rate of stroke, compared to a decrease of 56% with antiplatelet therapy. Similar observations were also noted in the SOLVD (Studies of Left Ventricular Dysfunction) trial (Anonymous, 1991a). While these data appear to support the use of anticoagulation for stroke prevention in low EF patients, antithrombotic therapy in this population must obviously target systemic vascular disease, including both cardiovascular and cerebrovascular events.

The appropriate antithrombotic therapy for these patients remains controversial, though three trials (two recently completed, one ongoing at the time of this writing) should provide some much needed insight. The WASH (Warfarin/Aspirin Study in Heart Failure) trial was an open-label, randomized controlled trial comparing no antithrombotic therapy, aspirin (300 mg/daily) and adjusted-dose warfarin (target INR 2.5) in patients with an EF of less than 35% (Cleland et al., 2004). In WASH, 270 patients were followed for a mean duration of 27 months, with a composite primary outcome of death, MI, or stroke. There was no difference noted in the primary outcome for either treatment arm, though there were significantly more patients in the aspirin arm hospitalized for worsening heart failure. The WATCH (Warfarin Antiplatelet Trial in Chronic Heart Failure) study was designed to compare aspirin, clopidogrel, and warfarin in patients with EF of less than 35%, but was unfortunately stopped prematurely given poor enrollment (around 1,500 of a planned 4,500), and thus is not sufficiently powered to evaluate the impact of these treatment arms of the composite primary endpoint of death, stroke, or MI (Massie et al., 2004). Unpublished analysis (presented in abstract form) did note a significantly lower rate of stroke in the warfarin arm compared to aspirin or clopidogrel, without apparent benefit with regard to the primary outcome measure. The available data from the WATCH study will likely be re-evaluated with results from the ongoing WARCEF (Warfarin Versus Aspirin in Reduced Cardiac Ejection Study). This double-blinded trial (Pullicino et al., 2006) plans to randomize over 2,800 patients with an EF of less than 35% to either warfarin (target INR 2.5–3.0) or aspirin (325 mg/day), with a primary outcome measure of the 3- to 5-year event-free survival from death or stroke (ischemic or hemorrhagic).

Current guidelines for antithrombotic therapy in patients with congestive heart failure/low EF are based primarily upon observational studies, though ongoing analyses of the WASH, WATCH, and forthcoming WARCEF trials will no doubt heavily influence future modifications. Multiple societies, including the ACCP (Harrington et al., 2004), ACC/AHA (Antman et al., 2004), European Society of Cardiology (Swedberg et al., 2005), and Heart Failure Society of America (HFSA) (Anonymous, 1999), have recently published independent recommendations. In general, all recommend anticoagulation for patients with symptomatic heart failure and concurrent atrial fibrillation, mobile left ventricular thrombus, or previous thromboembolism. Currently, only the HSFA guidelines specifically recommend anticoagulation for heart failure patients with an EF of less than 35% (the target population for the WATCH and WARCEF trials). Overall, all guidelines recommend that a patient with heart failure who suffers a cardio-embolic stroke should receive anticoagulation for the prevention of recurrent stroke (i.e., secondary prevention). The utility of anticoagulation of the primary prevention of stroke in heart failure patients will hopefully be addressed by the WATCH and WARCEF trials.

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Chapter 37

Cervical artery dissections

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37.1. Incidence

The incidence of cervical artery dissections (CAD) can only be examined with community studies. After exclusion of traumatic cases, the Rochester (Schievink et al., 1993) and Dijon (Giroud et al., 1994) community-based studies found average annual incidence rates of 2.6 CAD per 100,000 (3.5 per 100,000 over 20 years of age), and 2.9 internal carotid artery dissections (ICAD) per 100,000 inhabitants, respectively. In Rochester, this incidence was one-third of the annual incidence rate of aneurysmal subarachnoid hemorrhage (Broderick et al., 1989), but in Dijon ICAD was more frequent, the incidence of aneurysmal subarachnoid hemorrhage being 2.2 per 100,000 (Giroud et al., 1994). In Dijon, ICAD accounted for 2% of all strokes collected in the same period, and 10.1% of stroke patients less than 50 years of age. However, incidence rates of 2.2 and 2.9 new cases per 100,000 inhabitants per year are likely to be underestimated, because patients with CAD who never have ischemic events (Gobert et al., 1996; Mokri et al., 1996) are not included in stroke registries. Moreover, CAD leading either to very severe strokes with early death, or very mild and non-specific symptoms, are likely to remain undiagnosed in many cases. Therefore, the true incidence rate of CAD is likely to be much higher than 3 cases per 100,000 inhabitants per year.

Hospital-based studies suffer recruitment bias because they do not take into account patients who are not hospitalized and also because they are usually conducted in specialized centers which may recruit specific types of patients. CAD accounts for 1–2.5% of all strokes admitted in specialized centers (Biller et al., 1986; Bogousslavsky and Regli, 1987; Leys et al., 2002), and for up to 22% of cerebral infarcts occurring in young adults (Adams et al., 1982; Biller et al., 1986; Cronqvist et al., 1986; Bogousslavsky and Regli, 1987; Leys et al., 2002).

37.2. Causes

Traumas and primary diseases of the arterial wall are the main identified causes of CAD (Schievink et al., 1993, 1994a; Leys et al., 1995). It can therefore be divided into "traumatic" and "spontaneous" CAD (Mokri et al., 1986). Most cases in practice are spontaneous, but almost all studies on CAD have been conducted on patients admitted to stroke units or in neurological departments, leading to an underestimation of traumatic cases. The pathophysiology of non-traumatic CAD remains unknown, but the most likely hypothesis is a genetic predisposition, CAD being triggered by an infection or a minor trauma (Schievink et al., 1994c; Grau et al., 1999; Brandt et al., 2001; Guillon et al., 2003). In most CAD patients, no cause can be clearly identified.

37.2.1. Trauma

Neurological symptoms other than pain occur usually several days or weeks after injury (Mas et al., 1987; Rae-Grant et al., 1989; Quint and Spickler, 1990; Hinse et al., 1991; Tulyapronchote et al., 1994; Fletcher et al., 1995). Sudden stretching of a cervical artery resulting from trauma or strenuous effort can induce an intimal tear. Strangulation, car crash, hyperextension injury, electrocution, and chiropractic maneuvers are the main traumas reported by patients with CAD (Mokri et al., 1986; Leys et al., 1987; Mas et al., 1987, 1992; Hart, 1988; Young et al., 1991; Josien, 1992).

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The influence of chiropractic maneuvers seems more important in vertebral artery dissections (VAD) than in ICA dissections (Dziewas et al., 2003). The incidence of VAD after manipulation has been estimated at 1 in almost 6 million cervical manipulations (Haldeman et al., 2002a). Before 45 years of age, vertebrobasilar strokes are five times more likely to occur (95% CI: 1.32–43.87) in patients who have visited a chiropractor within 1 week of the stroke than controls (Rothwell et al., 2001), but this association disappears after 45 years. CAD may occur at any point in the course of manipulations (Haldeman et al., 2002b), and with any method of manipulation (Haldeman et al., 2002b). If this result supports the hypothesis of an association in young adults, there are several potential sources of bias, and no proof that CAD is the link between manipulation and stroke. However, similar results were found in another study, where VAD were independently associated with manipulations within 30 days (OR 6.62; 95% CI 1.4–30) after adjustment on neck pain (Smith et al., 2003). A causal relationship between cervical manipulations and CAD is therefore likely, but the absolute risk is probably low. Moreover, there is no prospective cohort study proving the relationship, most reports being case reports or small series, or case-control studies. It is possible that the patient was seeking neck manipulation due to neck pain already caused by CAD. However, one should recommend avoiding manipulations in patients with a history of CAD, and also when the reason why the patient has neck pain is not clear.

The type of trauma differs between VAD and ICAD. In ICA dissections, the mechanism of injury includes usually hyperflexion of the neck and rotation, stretching the ICA against the transverse processes of C2 and C3 vertebrae, or severe neck flexion compressing the ICA between the cervical column and the angle of the mandible. A prominent styloid process may injure the ICA during severe rotations of the neck, either steady or abrupt (Montalbetti et al., 1995). In VA dissections, the prominent mechanism is rotation of the neck, while flexion and extension play a minor role.

There is no large study evaluating the rate of CAD in patients with cervical spine traumas. However, a systematic evaluation of vertebral arteries by MRA and MRI in 47 patients admitted to orthopedic surgery, found significant lesions in 13 vertebral arteries (2 in the same patient), of which 4 were dissections, and 9 were occlusions without proof of a dissection (Parbhoo et al., 2001). None resulted in neurological deficits (Parbhoo et al., 2001). Although this study suffered severe potential bias it suggests that CAD may be frequent in patients with neck traumas severe enough to be admitted to an orthopedic surgery department, but usually remain silent.

The role of trivial traumas remains disputable. Many patients do not describe clear traumas, but a variety of minimal traumas that are often encountered in everybody in the daily life: forceful coughing, sport activities, sexual intercourse, sustained head rotation, sleeping in the wrong position, prolonged neck extension when painting a ceiling have all been described (Hart and Easton, 1983). These traumas are frequent during the few weeks preceding the clinical symptoms other than pain. A causal relationship is rarely proven, and a recall bias cannot always be excluded.

37.2.2. Pre-existing disorders of the arterial wall

37.2.2.1. Connective tissue disorders

Connective tissue disorders that may predispose to CAD (Mas et al., 1987, 1992; Mokri et al., 1987; Schievink et al., 1994a) are Ehlers–Danlos type IV syndrome, Marfan's syndrome, osteogenesis imperfecta, cystic medial necrosis, and pseudoxanthoma elasticum.

37.2.2.2. Fibromuscular dysplasia

Fibromuscular dysplasia is found in up to 20% of patients with CAD (Hart and Easton, 1983; Mokri et al., 1986). Fibromuscular dysplasia of renal arteries, which may lead to renal infarction (Amarenco et al., 1994), is occasionally associated with CAD (d'Anglejan Chatillon et al., 1990; Amarenco et al., 1994), suggesting a systemic artery disease.

37.2.2.3. Arterial tortuosities

In large series, slight tortuosities are present in 11–31% of subjects and extreme tortuosity are found in 3–12% (Sturzenegger et al., 1993; Ben Hamouda-M'Rad et al., 1995; Guillon et al., 1999). They are more frequent in patients with aneurysmal forms of CAD (Guillon et al., 1999). Frank loops in the artery at sites of CAD have been described (Barbour et al., 1994).

37.3. Risk factors

37.3.1. Demographic factors

CAD typically occurs in young adults with a mean age between 40 and 45 years, without clear gender difference (Schievink et al., 1994a; Leys et al., 1995; Touze et al., 2003b). They may sometimes occur in teenagers and children, especially after local injuries through the mouth. However, it is likely that CAD may also occur later in life but remains underdiagnosed, one-third of patients being older than 60 years in the Hanover study (Ahl et al., 2004).

37.3.2. Seasonal factors

A prominence of CAD in autumn has been found in the Rochester study, but needs confirmation (Schievink et al., 1998). Seasonal variations may be explained by seasonal variations in upper airway infections.

37.3.3. Factors leading to extracellular matrix modifications

The role of genetic predisposing factors, and especially that of genes coding for proteins of the extracellular matrix (Brandt et al., 2001; Brandt and Grond-Ginsbach, 2002; Grond-Ginsbach et al., 2002a, b; Lichy et al., 2002), is currently under investigation in several centers. However, many genetic studies conducted until now were negative, but none of them could detect a "reasonable" relationship between an allele and CAD, with odds ratios between 1.5 and 2.0.

Connective tissue abnormalities have been reported in dermal biopsies of CAD patients, with structural defects of the arterial wall (Brandt et al., 2001). Völker et al. (2005) found vacuolization of smooth muscle cells in superficial temporal arteries of CAD patients, as compared with controls, supporting the hypothesis that CAD patients have a systemic arteriopathy. This hypothesis is also supported by ultrastuctural studies of cervical arteries and studies performed on endarterectomy materials (Peters et al., 1995), and by abnormal elastin or fibrillin in cultures of dermal fibroblasts, which is more frequent in CAD patients than in controls. Deficiencies of protease inhibitors such as alpha1-antitrypsin have been suggested as predisposing to CAD (Schievink et al., 1994c; Vila et al., 2003), not in all studies (Grond-Ginsbach et al., 2004), but in small groups of patients.

Matrix metalloproteinases (MMPs) degrade extracellular matrix proteins, and can lead to vascular damage. However, a study on two different MMP-9 DNA polymorphisms found no differences in the allelic distribution of either polymorphism between patients and controls, but again, the statistical power was low (Wagner et al., 2004). No clear association has been found between CAD and collagen III (COL3A1 gene) (Kuivaniemi et al., 1993; Van den Berg et al., 1998; Von Pein et al., 2002), and collagen V (COL5A2 gene) (Grond-Ginsbach et al., 2002b). However, these studies included less than 50 patients and were underpowered.

Hyperhomocysteinemia may represent a potential risk factor for CAD, leading to structural abnormalities of the arterial wall and increasing the susceptibility to mechanical stress (Pezzini et al., 2002b). Increased total plasma homocysteine levels (Gallai et al., 2001; Pezzini et al., 2002a), and the TT MTHFR genotype may represent risk factors for CAD (Gallai et al., 2001; Pezzini et al., 2002a).

37.3.4. Endothelial dysfunction

Our group studied flow-mediated arterial dilation and found an impaired endothelium-dependent vasodilatation in CAD patients, but not in matched ischemic stroke patients without CAD, suggesting that an underlying abnormality of the arterial wall layers with endothelial dysfunction may predispose to CAD (Lucas et al., 2004).

37.3.5. Modification of elastic properties of the arterial wall

Aortic root diameter enlargement (Tzourio et al., 2002) has been reported in patients with CAD, suggesting a widespread modification of the arterial walls. Calvet et al. (2004) studied the elastic properties of a cervical artery, the common carotid artery, and a distal muscular artery, and found that carotid arteries, but not the aorta and radial artery, displayed abnormal elastic properties in CAD patients: higher stiffness of carotid wall material and circumferential wall stress could increase the risk of dissection in these patients.

37.3.6. Migraine

Migraine is associated with an increased stroke risk. The association between migraine and CAD has been reported in recent studies. Migraine is 3.6-fold (95% CI: 1.5–8.6) more frequent in patients with CAD (Tzourio et al., 2002). This finding supports the hypothesis that an underlying arterial wall disease could be a predisposing condition for migraine. Studies of the relationship between migraine and dissection (Fisher, 1982; D'Anglejan-Chatillon et al., 1989; Tzourio et al., 2002) may suffer several sources of bias (Leys et al., 1995) and some migrainous infarcts might actually be due to CAD (Bousser et al., 1985).

37.3.7. Familial disorders

In patients with ICAD, the prevalence of a family history of CAD or cerebral aneurysm is of 18.2% versus 2.6% in controls (Majamaa et al., 1994); the prevalence of CAD and cerebral aneurysms is of 3.5% among the siblings of patients with CAD and 0.53% among those of controls.

37.3.8. Recent infections

Recent infections are potential risk factors for ischemic strokes and are also more frequent in CAD (Grau et al., 1999, 1997), independently of mechanical factors such as coughing, sneezing, or vomiting (Grau et al., 1997, 1999). Patients with ischemic stroke due to CAD have a higher frequency of infections over the subsequent 4 week period, and higher levels of ultra-sensitive C reactive protein, than ischemic stroke patients of other etiology (Guillon et al., 2003; Genius et al., 2005). The association between CAD and infections is stronger in cases of multiple dissections (Guillon et al., 2003; Genius et al., 2005).

37.3.9. Vascular risk factors

Other potential risk factors for dissection are pregnancy, oral contraceptives, smoking, and arterial hypertension, but these associations are not firmly established.

37.4. Pathology

The proportion of patients with VAD is approximately one-third of all CAD (Schievink et al., 1994a; Touze et al., 2003a).

37.4.1. Location of the dissection

The ICA is usually affected in the pharyngeal and distal segments, more than 2 cm after its origin; this location differs from that of atherosclerosis, which affects the first 2 cm or the siphon. VAD are usually located in the V1 or in the V3 segment of the VA (Caplan et al., 1985). The pharyngeal ICA and the V1 and V3 segments of the VA are mobile and less firmly anchored than other parts of these arteries.

Most cases of CAD are subadventitial; that is, they are located between the media and the adventitia or in the media itself; the thicker outer coats and supporting tissues probably limit the risk of bleeding. Patients with concentric mural hematoma are more likely to have ischemic events and cerebral changes on diffusion-weighted images, while patients with eccentric hematoma are more likely to have a non-ischemic clinical presentation, a normal cerebral MRI, and may even have normal ultrasound findings (Lanczik et al., 2005).

37.4.2. Origin of the mural hematoma

The hematoma may be the consequence of the penetration of blood through a primary intimal tear (Hart and Easton, 1983), or of a primary hemorrhage from the vasa vasorum, that may be the most frequent mechanism (Volker et al., 2005). Even a small tear in the intima can enlarge as the bloodstream burrows circularly, proximal and distal beneath the flap. Dissections may enter the main channel to create a double-barreled artery. The hematoma can extend to the skull base where it stops.

37.4.3. Consequences of the mural hematoma

37.4.3.1. Arterial lumen narrowing or occlusion

Cerebral ischemia occurs when the mural hematoma leads to a narrowing of the arterial lumen or in thrombo-embolic events. The blood stasis and the release of factors promoting thrombosis by the endothelium may lead to an intraluminal clot adherent to the intima which may extend up and lead to emboli (Lucas et al., 1998; Benninger et al., 2004).

37.4.3.2. Double channels

The intramural hematoma creates a false lumen, which may reconnect with the true arterial lumen distally, creating two parallel channels of blood circulation, separated by a long intimal flap.

37.4.3.3. Arterial wall enlargement and pseudo-aneurysm

The intramural hematoma may expand outwards and create a subadventitial aneurysmal sac. This aneurysm is formed within the media, and is connected with the true lumen. It may lead to the formation of thrombi. The enlargement of the external diameter of the artery may induce compression of the surrounding structures (Sturzenegger and Huber, 1993). In the upper cervical parapharyngeal space, lower cranial nerves have a close topographical relationship with the expanded carotid wall (De Broucker et al., 1994). In patients with upper cranial nerve palsies, dissection usually extends into the petrosal and cavernous segment. Other mechanisms of cranial nerve involvement are ischemia of the nerves due to compromised blood supply (Lasjaunias and Doyon, 1978; Lapresle and Lasjaunias, 1986), abnormal artery originating from the petrous or extrapetrous ICA supplying the nearby cranial nerves, or an ascending pharyngeal artery arising directly from the dissected ICA (Mokri et al., 1992). Interruption of the nutrient arteries supplying the oculomotor nerves could also explain their involvement by dissection of the ICA. A large aneurysm of the VA with intraspinal or intracranial extension can lead to a compression of the spinal cord, brainstem, cranial nerves (Detwiler et al., 1987), or even cervical roots (Ross et al., 1988).

Bleeding is not an usual consequence of CAD. Some patients with dissections have pseudo-aneurysms with limited rupture into the space surrounding the artery. In a case of subarachnoid hemorrhage associated with a dissection of the extracranial VA an associated transmural dissection of the intracranial VA is likely to be present (Biousse et al., 1994a).

37.4.3.4. Coexistence of stenosis and pseudo-aneurysm

The above-mentioned signs (stenosis and arterial wall enlargement) may coexist. Occasionally, patients have multifocal regions of dissections of various ages and bilateral aneurysms (Caplan et al., 1988).

37.5. Clinical manifestations

Paucisymptomatic cases of CAD are frequent and underdiagnosed. However, the screening of CAD being easier nowadays because of the availability of non-invasive techniques, these cases are more often recognized than 20 years ago when conventional angiography was the only way to make a diagnosis of CAD.

CAD may even remain silent (Sturzenegger et al., 1993; Schellinger et al., 2001), either because there is no symptoms at all, as seen in patients with a symptomatic CAD in one vessel and asymptomatic dissections in other vessels, or because they occur after a severe trauma and are masked by more severe lesions. The possibility of CAD in patients with severe traumas involving the neck, especially in cases of associated head trauma and coma, should be known and a systematic screening with ultrasound and MRI should be performed (Sturzenegger et al., 1993; Schellinger et al., 2001).

37.5.1. Dissections of the internal carotid artery

37.5.1.1. Pain

Pain is the initial symptom of ICAD in 60% of patients, and occurs in 75% of them (Biousse et al., 1992, 1994b). It may be isolated (Biousse et al., 1992, 1994b), associated with an ischemic event, or associated with local symptoms, especially Horner's syndrome. Pain is usually ipsilateral to the dissection, lasts up to 1 month (Labauge et al., 1971), and is usually described as a throbbing headache or sharp pain located in the neck, jaw, pharynx, or face. A recurrence of neck pain suggests extension (Ehrenfeld and Wylie, 1976) or recurrence of CAD (Leys et al., 1995). However, headache is not specific and can be seen in other causes of cerebral ischemia. Headache may be acute and misdiagnosed as symptomatic of a subarachnoid hemorrhage (Biousse et al., 1994a), or may meet criteria for migraine attack (Goodman et al., 1983), or even hemicrania continua (Rogalewski and Evers, 2005).

37.5.1.2. Ischemic events

TIA are probably due to luminal compromise with distal hypoperfusion (Lanczik et al., 2005) while severe strokes are more likely to be embolic (Lucas et al., 1998; Benninger et al., 2004).

37.5.1.3. Peripheral or sympathetic nerves injury

An ipsilateral Horner's syndrome is present in half of all patients with ICAD (Sturzenegger and Huber, 1993), and is the consequence of a sudden enlargement of the ICA, stretching or compressing sympathetic fibers (Panisset and Eidelman, 1990).

Two-thirds of spontaneous ICA dissection revealed by lower cranial nerve deficits are not associated with cerebral ischemia (Sturzenegger and Huber, 1993; Baumgartner et al., 2001). In stroke patients slight cranial nerve palsies may be unrecognized or misinterpreted (Gobert et al., 1996), and CAD occurring without ischemic event are not always recognized (Sturzenegger and Huber, 1993; Baumgartner et al., 2001).

In order of frequency, the affected cranial nerves are XII, IX, X, XI, V, VII, VI, and III. The involvement of the fifth cranial nerve is associated with an extension of the dissection to the cavernous segment. Oculomotor palsies are rare; of 155 patients with spontaneous dissections of the ICA, only 4 had an oculomotor palsy (Schievink et al., 1993). Most patients recover within 2 to 4 months (Sturzenegger and Huber, 1993; Baumgartner et al., 2001). In any patients with lower cranial nerve palsies, CAD should be considered as a possible diagnosis.

37.5.1.4. Pulsatile tinnitus

Pulsatile tinnitus, audible bruit, or noise matching the heartbeat, are other possible presentations. They may sometimes be isolated.

37.5.2. Dissections of the vertebral artery

37.5.2.1. Pain

Pain occurring hours before stroke is often the first and sometimes the only symptom of VAD (Caplan et al., 1985). It consists of cervical or neck pain, located at the level of the VAD. However, headache is not specific and may occur in other causes of vertebrobasilar infarcts.

37.5.2.2. Ischemic events

The most frequent clinical deficit resulting from VAD is a lateral medullary syndrome (Caplan et al., 1985;

Leys et al., 1987) but various other brainstem or posterior cerebral artery infarcts have also been reported (Linden et al., 1992). TIA are less frequent in VAD than in CAD, and spinal infarcts are possible in bilateral VA dissections (Labouret et al., 1993).

37.5.2.3. Peripheral nerve injury

A few cases of VAD revealed by peripheral motor deficits in the ipsilateral upper limb (Bergqvist et al., 1997; Hundsberger et al., 1998; Crum et al., 2000), or severe intermittent pain in the upper arm (Linden et al., 1992; Giroud et al., 1993) have been reported.

37.5.2.4. Subarachnoid hemorrhage

Subarachnoid hemorrhage may occur when the dissection extends into the intracranial portion of the artery (Biousse et al., 1994a).

37.6. Diagnosis

Non-invasive techniques should be used to detect, monitor, and follow-up CAD, because of the usually favorable outcome, and the potential risks of catheter angiography. Various techniques are available, and have different diagnostic values for stenosis, occlusions, pseudo-aneurysms, and underlying vascular pathologies. Nowadays, the diagnostic strategy should be based on ultrasonography completed by another examination, which should be MRI where possible, or helical CT in cases of contraindication for MRI. There is almost no reason to perform a catheter angiography in CAD.

37.6.1. Ultrasonography

Ultrasonographic evaluations include Duplex sonography associated with Doppler color flow imaging, and transcranial Doppler examination (TCD). Ultrasound is also useful for follow-up. TCD provides information on collaterals; progressive hemodynamic changes frequently occur over time in communicating arteries, which become patent within a few hours (Kaps et al., 1990). Ultrasound is a sensitive and reliable tool for early detection of ICAD, and a lower-level VAD.

37.6.1.1. ICA dissections

Hemodynamic features (Hennerici et al., 1989; Steinke et al., 1994; Srinivasan et al., 1996; Droste et al., 2001) include:

1. High-resistance pattern in the common carotid artery;
2. Decreased or reverse flow in the ophthalmic artery;
3. High-amplitude signal with severely reduced systolic Doppler frequencies and alternating flow directions at the level of the luminal narrowing, due to abnormal vessel-wall pulsations and bidirectional movements of the blood column;
4. Slight pure systolic flow of short duration traced along the course of the ICA;
5. High incidence of intracranial microemboli in the MCA distal to ICAD, with a significant correlation with the risk of stroke;
6. Echographic signs of ICAD (Steinke et al., 1994; Srinivasan et al., 1996) are:
   - Tapering of the ICA lumen beginning well above the bifurcation, with or without thrombus formation;
   - Sometimes a double lumen with an irregular membrane crossing the lumen;
   - Absence of atheroma. An ICA occlusion located above the bifurcation in a patient free of atheroma suggests dissection.

Ultrasonography should be performed at an early stage to detect the characteristic pattern of dissection and to provide diagnostic clues. Dissection is a dynamic process that may cause rapid lumen obliteration but also early recanalization or fluctuating or slowly progressive mural hematoma. As a result, ultrasound findings may greatly vary over time in the same patient.

37.6.1.2. VA dissections

The most frequent but non-specific finding in VAD is a high-resistance signal in the proximal segments, as reported in ICAD (Hennerici et al., 1989). In addition, a localized increase in diameter with decreased pulsatility and occasional intravascular echoes has been described. The dissection cannot always be directly visualized. In cases of direct stenosis detection (high blood flow velocity) or indirect signs of stenosis (severely reduced or absent ipsilateral blood flow velocity, increased pulsatility index, increased contralateral blood flow velocity), no further information about its cause can be obtained. The diagnostic value of ultrasonographic investigations in VAD is much lower than in ICAD, and normal findings do not exclude VAD.

37.6.2. Magnetic resonance imaging

MRI is an important diagnostic tool, and is also useful for the follow-up of CAD (Lucas et al., 2000a).

37.6.2.1. Magnetic resonance angiography (MRA)

MRA provides a non-invasive visualization of the lumen (Leclerc et al., 1999). The combined use of ultrasonography with MRA providing angiogram-like

images (Rother et al., 1995; Leclerc et al., 1999). Röther (1995) found a sensitivity of MRA for correctly diagnosing distal VAD of 97%, whereas the specificity was 98.9%; the sensitivity of Doppler ultrasound was 76.4%, with a specificity of 98.9%.

The diagnosis of CAD on MRA is based on location, description and evolution of the arterial changes. The MRA signs of dissection are associations at various degrees of arterial stenosis (Fig. 37.1) or occlusion (Fig. 37.2), aneurysm (Figs. 37.3 and 37.4), intimal flap, and double lumen.

ICAD starts at 3 cm above the bifurcation or more distally. Recognition of a low-grade narrowing of the lumen may be difficult. In subintimal dissections, the mural hematoma protrudes the intima into the vessel lumen and produces a variable degree of stenosis up to occlusion. Stenotic or occlusive forms of dissections are easily found with MRA. The arterial changes found on MRA are similar to those that had been described previously with catheter angiography: (1) a long irregular stenosis initiating distal to the carotid sinus, and usually extending to the skull base, described as a "string sign" (Figs. 37.5 and 37.6); and in occlusive types, visualization of an enlarged arterial wall due to the mural hematoma. Occlusions of the ICA differ from atherosclerotic occlusions in that they start more than 2 cm distal to the origin of the ICA,

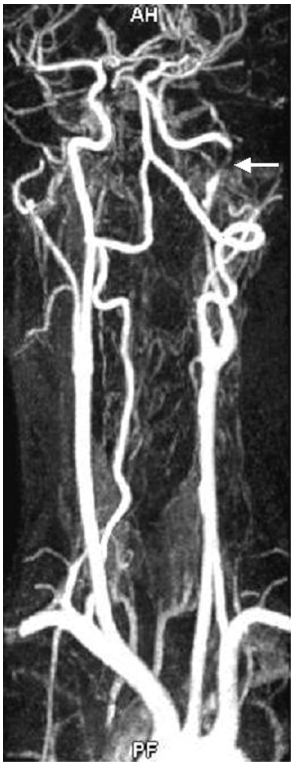

Fig. 37.1. Magnetic resonance angiography. Stenotic form of vertebral artery dissection (arrow).

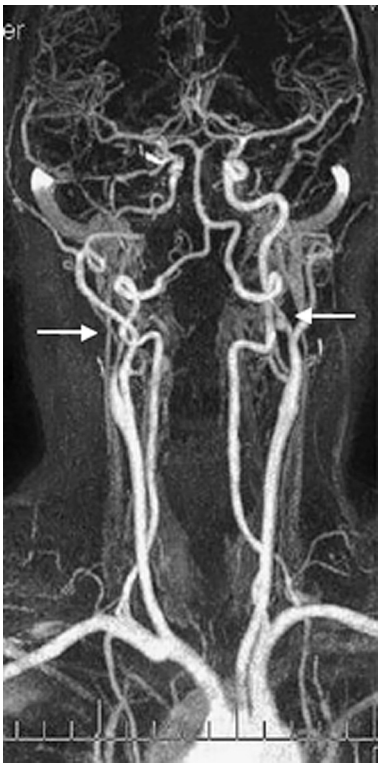

Fig. 37.2. Magnetic resonance angiography. Bilateral internal carotid artery dissection. Occlusive type on the right side (arrow); stenotic type on the left (arrowhead).

spare the siphon and have a gradually tapering segment that ends in the occlusion. However, occlusion and stenosis may be observed in retrograde thrombus in cases of embolic occlusions of the siphon, fibromuscular dysplasia, radiation-induced stenosis, and arterial hypoplasia. Double lumen or intimal flaps are typical of dissection, but rarely seen. Aneurysmal sacs or outpoutchings are other angiographic findings; they are either saccular or fusiform, located at the skull base, and associated with a narrowed or a dilated portion of the artery. When the vessel is occluded, the etiology of the occlusion remains unrecognized until the hematoma is proven.

37.6.2.2. Axial MRI sequences

Axial MRI sequences show the mural hematoma, the degree of wall expansion, and the relationship with the surrounding tissues (Maitland et al., 1983; Goldberg et al., 1986; Leclerc et al., 1998, 1999; Zuber et al., 1999). The typical MRI picture is (Maitland et al., 1983; Goldberg et al., 1986; Leclerc et al., 1998, 1999; Zuber et al., 1999):

1. A narrowed eccentric hypointensity (signal void), corresponding to the remaining flow in the lumen (Figs. 37.7 and 37.8).

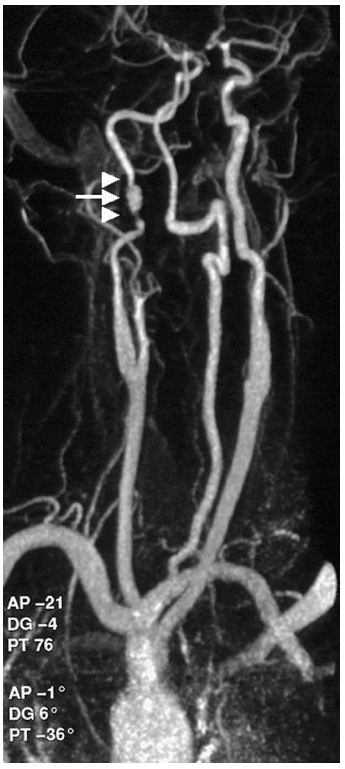

Fig. 37.3. Magnetic resonance angiography. Aneurysmal form of dissection. The aneurysmal portion of the artery (arrow) is separated by two areas of stenosis (arrowheads).

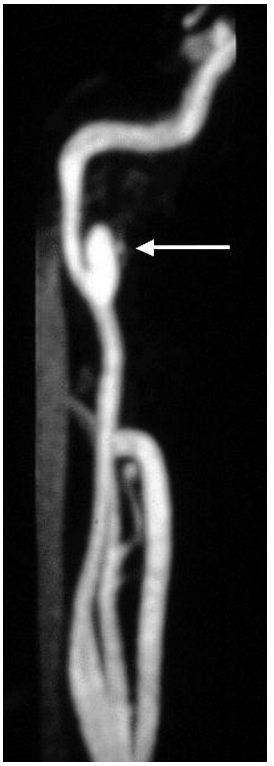

Fig. 37.4. Magnetic resonance angiography. Residual aneurysmal 3 months after dissection (arrow).

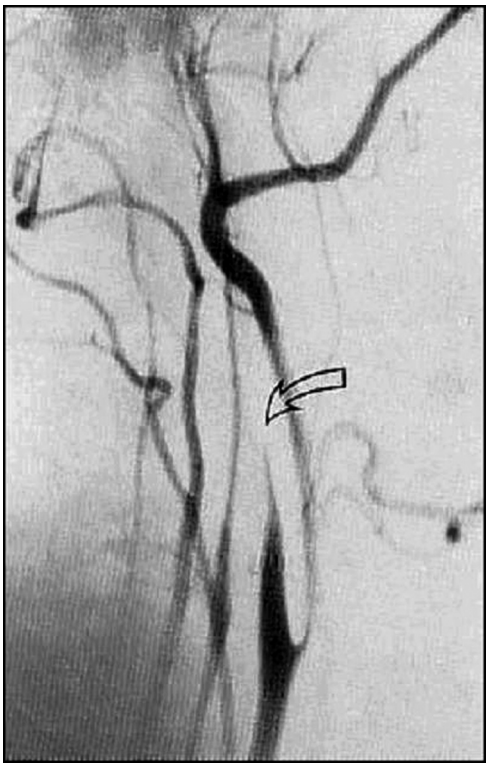

Fig. 37.5. Catheter angiography. Occlusion of the internal carotid artery more than 2 cm after the bifurcation (arrow).

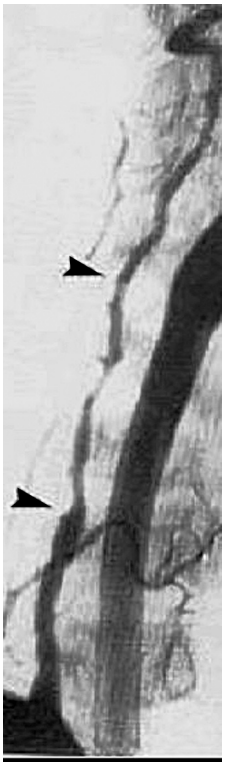

Fig. 37.6. Catheter angiography. Long stenosis of the vertebral artery (arrowheads).

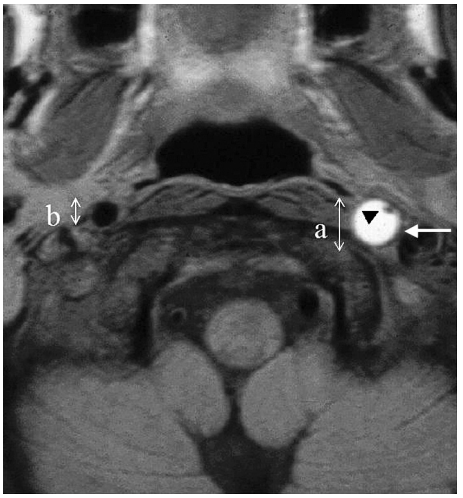

Fig. 37.7. Magnetic resonance imaging. Mural hematoma (arrow) of the left internal carotid artery with an eccentric narrowed lumen (arrowhead). Enlargement of the external diameter of the dissected artery (a) as compared with the normal one (b).

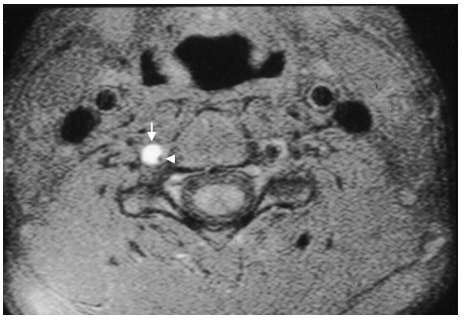

Fig. 37.8. Magnetic resonance imaging. Mural hematoma (arrow) of the left vertebral artery with an eccentric narrowed lumen (arrowhead).

2. A semilunar signal hyperintensity corresponding to the mural hematoma (Figs. 37.7 and 37.8). Contrary to flow signals, the semilunar signal hyperintensity remains unchanged on T1- and T2-weighted images. MRI is the method of choice to detect small mural hematomas. In subadventitial dissections, the resulting hematoma can compress adjacent structures such as lower cranial nerves without causing relevant vessel narrowing.
3. Routine MRI with axial slices is a sensitive technique for the diagnosis of dissection of the ICA, but may appear normal in a few patients. However, the determination of the percentage lumen reduction and, in occlusive dissections, the differentiation between a mural hematoma and an extensive intraluminal clot, is sometimes difficult. The sensitivity of MRI to detect dissections is lower for VA dissections than for ICA dissections.

37.6.3. Helical computed tomography

Helical CT scan is a sensitive procedure when directed by a prior MRA, but cannot be considered as a reliable screening technique (Leclerc et al., 1996, 1998). Signs of dissection are (Leclerc et al., 1996, 1998): presence of a stenosis or occlusion, eccentric lumen, mural thickening, aneurysm, increased external diameter of the artery, and annular contrast enhancement (so-called "target picture").

In occlusive forms of dissections, the enlargement of the dissected artery is the best diagnostic criterion (Leclerc et al., 1996). Helical CT has however several limits (Leclerc et al., 1996):

1. The need of contrast media injection;
2. High level of thyroid irradiation that, according to the European rules, must be justified before being adopted, especially when an alternative technique having the same objectives but involving no exposure to ionizing radiation, such as MRI, is available (directory 97/43 Euratom from the European commission);
3. The hematoma is seen only during the earliest stage of CAD and its density returns to that of the surrounding structures within a few days;
4. Artifacts, especially in VAD, at the skull base, where the diameter of the artery is small, and tortuosities present.

It is, nevertheless, a reliable method for the diagnosis and for the follow-up of CAD (Leclerc et al., 1998). The development of modern multidetector CT techniques increases the potential of helical CT for the diagnosis and follow-up of CAD, especially useful when MRI is not feasible.

37.6.4. Catheter angiography

Catheter angiography has long been considered the gold standard for the diagnosis of CAD. However, non-invasive techniques are not dangerous and show directly the intramural hematoma, therefore they have replaced catheter angiography in almost all patients.

37.7. Treatment

37.7.1. Anticoagulation

There is no randomized trial that has evaluated the potential of anticoagulation to reduce the risk of early recurrence of ischemic stroke in CAD patients. No

reliable comparisons of antiplatelet drugs or anticoagulants with control are available. The Cochrane analysis (Lyrer and Engelter, 2003, 2004) found 26 eligible studies including 327 patients (who either received antiplatelet drugs or anticoagulants) to be included in a comparative analysis: there was no significant difference in odds of death comparing antiplatelet drugs with anticoagulants (OR: 1.59; 95% CI 0.22–11.59), and no difference in the odds of being dead or disabled (OR 1.94; 95% CI 0.76–4.91). Few intracranial hemorrhages (0.5%) were reported for patients on anticoagulants, and none for patients on antiplatelet drugs.

However, to show a 50% reduction risk of early recurrence with heparin over aspirin, with an alpha risk set at 5% and a beta risk set at 10%, almost 10,000 patients should be recruited, which is not realistic. The sample size is much greater for a more realistic hypothesis of 20% reduction risk. Therefore, in the absence of randomized trials, heparin prescription is based on the supposed pathophysiological mechanism of ischemia in CAD patients, which is likely to be embolic in most cases (Benninger et al., 2004; Lucas et al., 2004). However, this lack of proof makes the prescription of heparin less appropriate in cases with a high risk of bleeding, as in patients with large infarcts. Biousse (1995) found that, in ICAD, stroke usually occurs in the first few days after onset, suggesting that preventive treatments should be initiated as early as possible. Anticoagulants do not seem to increase the extent of the intramural hematoma, a major theoretical concern, but delayed occlusions have been reported under heparin in a few cases (Dreier et al., 2004). The good clinical outcome after discharge does not allow potentially dangerous treatments such as long-term oral anticoagulants for more than 3 months.

37.7.2. Antiplatelet agents

Antiplatelet agents, especially aspirin, are recommended at the acute stage in large infarcts, or after the acute stage, when anticoagulation is stopped, especially in cases of underlying arteriopathy or a residual aneurysm.

37.7.3. Thrombolytic therapy

The question of whether, in patients admitted within 3 hours of stroke onset, rtPA increases the volume of the intramural hematoma (and therefore hemodynamic failure) is not completely resolved. However, reports of small series and isolated case reports suggest that rtPA is safe in patients with CAD (Derex et al., 2000; Arnold et al., 2002; Georgiadis et al., 2005).

37.7.4. Prevention of hemodynamic failure

Staying strictly bedridden during the first days of dissection, when TCD suggests a hemodynamic failure or when TIA occurs when standing up might prevent hemodynamic failure. However, this procedure is empirical and has not yet been tested in a randomized trial.

37.7.5. Surgery and stenting

Isolated cases of severe cerebral ischemia in patients with multivessel dissections have been successfully treated by stenting at the acute stage (Coric et al., 1998), alone (Cohen et al., 2003), or in combination with endovascular thrombolysis (Abboud et al., 2005). No randomized data are available. This technique can only be recommended in experienced centers, for severely affected patients.

The natural history of residual aneurysms is to resolve or to improve in almost 50% of cases and, when they persist, they never rupture (Hart and Easton, 1983; Mas et al., 1987; Caplan et al., 1988; Hart, 1988; Youl et al., 1990). Therefore, there is no scientific rationale for an invasive approach of CAD, even in the case of aneurysms.

37.8. Outcome

37.8.1. Mortality

The mortality rate in patients with CAD mainly depends on the severity of the initial ischemic episode. Follow-up studies suggest a fairly good overall prognosis in adults with low mortality rates (Bogousslavsky et al., 1987; Pozzati et al., 1990; Schievink et al., 1994a, b; Leys et al., 1995; Touze et al., 2003a). However, we cannot exclude an underestimation of the mortality rate in patients with CAD, because it is likely that, among young patients with a severe ischemic stroke and an early death, a few cases of CAD are not identified.

37.8.2. Recurrent ischemic events

In 105 patients with CAD followed for a mean of 36 months, the rate of recurrent stroke was only 1.9% (Leys et al., 1995). More recently, Touze et al. (Pozzati et al., 1990; Schievink et al., 1994b; Touze et al., 2003a) assessed the risk of stroke, transient ischemic attack (TIA) and recurrence of CAD after a first CAD in a multicenter French cohort study of 459 consecutive patients. After a mean follow-up of 31 months, 4 (0.9%) of 457 survivors had had a recurrent ischemic

stroke attributable either to the initial CAD that did not completely recover, or a recurrent CAD. A Swiss study (Kremer et al., 2003) published at the same time provided similar findings with an annual rate of ipsilateral ICA stroke of 0.7% and of any stroke of 1.4% (Kremer et al., 2003). There is no significant influence of the persistence of arterial stenosis or occlusion on the risk of recurrent stroke after CAD (Kremer et al., 2003) or on functional outcome (Caso et al., 2004). These follow-up studies had different objectives, designs, and endpoints, but they all suggest that patients with a first CAD have a low risk of recurrent ischemic events.

37.8.3. Recurrent dissections

Bogousslavsky (1987) found only 1 recurrent CAD in 30 patients followed for a mean of 3.2 years. Pozzati (1990) found no recurrent CAD in 19 patients with occlusive dissection of the ICA followed for a mean of 8.2 years. Schievink (1994a) evaluated the risk of recurrent CAD in arteries which were not initially involved. Of 200 patients with a mean follow-up of 7.4 years, only 4 developed recurrent CAD within 1 month to 8.6 years, leading to a cumulative rate of recurrent CAD of 12% after 10 years. Of 105 patients with CAD followed for a mean of 36 months, we found recurrent CAD in 3 patients (Leys et al., 1995), leading to a cumulative rate close to that found in the Rochester (Schievink et al., 1994a) and the Bern (Bassetti et al., 1996) studies. Family history of CAD (Schievink et al., 1996) and connective tissue disorders (Leys et al., 1995), are associated with an increased risk of recurrent CAD.

37.8.4. Residual headache or cervical pain

Residual headache or cervical pain is frequent after CAD (Leys et al., 1995). Headache often meets the criteria for migraine (Leys et al., 1995). The mechanism of residual headache or cervical pain remains unknown. Although headache reported after endovascular procedures are usually very acute (Martins et al., 1993), they may share similar mechanisms with post-CAD such as mechanical stimulation of the arterial wall (stretching, distortion), local inflammatory changes, and vasodilatation in collaterals. Residual pain probably accounts for a part of the discrepancy that has been found in patients with VA dissections, between an usually good outcome in terms of standard stroke scales and quality of life (Czechowsky and Hill, 2002).

37.8.5. Radiological outcome

The angiographic outcome does not always parallel clinical outcome. In our previous study (Leys et al., 1995), reopening occurred in 55.6% of patients, a partial reopening in 2.2%, an aneurysm in 5.6%, and no reopening in 36.7%. In the Rochester study, 90% of stenoses and two-thirds of occlusions reanalyze, usually within 3–6 months (Schievink, 2001). Aneurysms are reported on angiography in up to one-third of patients with ICAD. They can occur after a few weeks or months, especially in cases of CAD with severe stenosis or occlusion masking the aneurysm. Some probably lead to cerebral emboli but this risk is not clearly established. Others heal spontaneously (Touze et al., 2001); however, in this case there is usually some degree of stenosis left on the previously dissected artery (Leclerc et al., 1998; Lucas et al., 2000a, b).

37.9. Conclusions

CAD is a leading cause of cerebral ischemia in young persons, but may also be revealed by other neurological signs as well as ischemia. It can easily be diagnosed by non-invasive techniques and catheter angiography should not be used as a diagnostic procedure anymore. Its occurrence is probably due to the coexistence of a pre-existing artery disease (connective tissue disorder, infection) and a trauma, but in most cases no cause can be identified. The outcome is usually very good, although a few cases with early death have been identified. The risk of recurrence is very low. In the absence of randomized trials, the most widely used therapy is anticoagulation, but many centers use aspirin. Except in very selected patients with severe acute ischemia, the excellent outcome of patients with CAD makes hazardous the use of any potentially dangerous procedures.

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Chapter 38

Intracerebral hemorrhage

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38.1. Epidemiology

Intracerebral hemorrhage (ICH) results from arterial bleeding directly into brain parenchyma. In defining the pathogenesis, risk factors, and clinical course of primary ICH, evidence suggests that the location of hemorrhage is important (Woo et al., 2002; Viswanathan et al., 2006). Deep hemispheric ICH (deep ICH) is a result of rupture of small arterioles most commonly in the putamen or thalamus (Mohr et al., 1978; Wiggins et al., 1978; Furlan et al., 1979; Kase et al., 1982; Kunitz et al., 1984) (Fig. 38.1A). Lobar intracranial hemorrhage (lobar ICH), which accounts for 33–42% of all ICH (Anderson et al., 1994; Massaro et al., 2002; Woo et al., 2002), results from rupture of small and medium-sized arteries in the hemispheric subcortical white matter and is most commonly associated with cerebral amyloid angiopathy (CAA) (O'Donnell et al., 2000) (Fig. 38.1B). Studies have demonstrated that the risk of recurrence may be as much as five times higher in lobar relative to deep ICH (O'Donnell et al., 2000; Bailey et al., 2001; Viswanathan et al., 2006).

Because the pathophysiologic differences between lobar and deep ICH were only recently appreciated, this distinction was not made in many early studies which evaluated risk factors for ICH. Thus, based on the available data, the risk factors for deep ICH (versus lobar ICH) are not yet fully defined. In the discussion that follows we will note those studies which have specifically made this distinction.

38.2. Incidence

Of those patients presenting with stroke, numerous North American and European studies have established the rate of ICH to be between 5% and 10% (Kurzke, 1969; Mohr et al., 1978; Sacco et al., 1984). In a consecutive series of 938 patients presenting with stroke in the National Institute of Neurological and Communicative Diseases and Stroke (NINCDS) Data Bank, primary ICH accounted for 10.7% of the cases (Kunitz et al., 1984). Population- or community-based studies from various other centers have been consistent with these figures. These include studies from Denmark (10.4%) (Hansen and Marquardsen, 1977), the Netherlands (9%) (Herman et al., 1980), Oxfordshire, UK (10%) (Bamford et al., 1990), and southern Alabama (8%) (Gross et al., 1984). Asian populations seem to have an increased proportion of stroke due to ICH (24–55%) (Kita et al., 1999; Yang et al., 2004). As with ischemic cerebral infarction, there is an increasing incidence with age (Sacco et al., 1984; Broderick et al., 1992).

Differences may exist in ICH incidence among different ethnic and racial groups. The incidence rates in white populations range between 7 and 11 cases per 100,000 (Furlan et al., 1979; Drury et al., 1984; Brott et al., 1986; Schutz et al., 1990; Broderick et al., 1992). Blacks have been noted to have a higher incidence rate as compared to whites in several studies. In a southern Alabama study (Gross et al., 1984) blacks had a rate of 32 per 100,000 versus 12 per 100,000 in whites. Similarly, a study from Cincinnati, Ohio showed a 1.4-fold increased risk of ICH in blacks compared to whites after adjusting for age and sex (Broderick et al., 1992). For those under 75 years old, the incidence was even greater (2.3-fold). A population of Hispanics in New Mexico had a higher incidence of ICH compared to non-Hispanic whites from the same population (34.9/100,000 versus 16.6/100,000) (Bruno et al., 1996). Similarly, a recent

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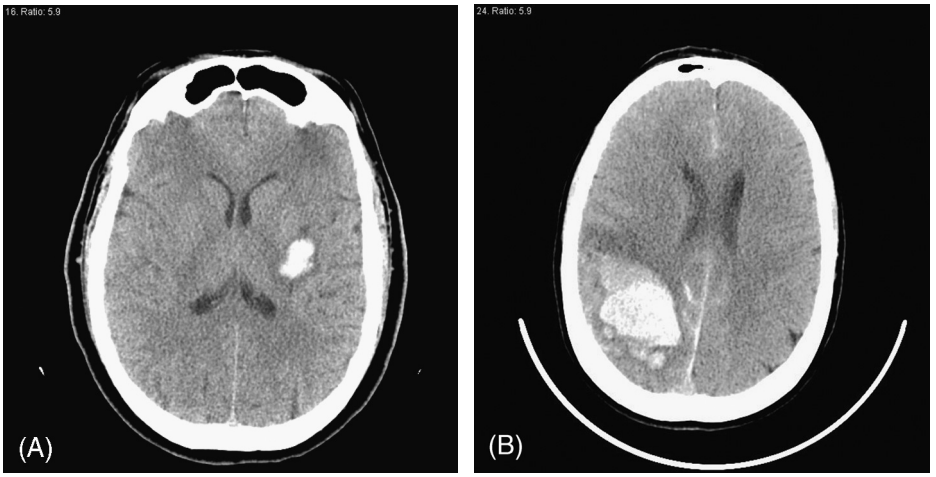

Fig. 38.1. (A) Deep hemispheric intracerebral hemorrhage. Left putaminal hematoma. (B) Lobar intracerebral hemorrhage. Right parietal hematoma.

population-based study in Nueces County, Texas showed that Mexican-Americans had an increased rate of ICH compared to non-Hispanic whites (age-adjusted risk ratio of 1.63) (Morgenstern et al., 2004). An increased incidence of ICH has been noted in Asian populations such as a study from Shibata, Japan (61/100,000) (Tanaka et al., 1981). The relative contributions of genetic and environmental factors to these different risks remain under investigation.

38.3. Risk factors

38.3.1. Hypertension

The prevalence of hypertension in different populations plays an important role in risk of ICH. Indeed, there has been a general decrease in the incidence of ICH worldwide, likely related to better control of blood pressure noted in populations in Sweden (Aurell and Head, 1964) as well as in Rochester, MN (Furlan et al., 1979; Garraway et al., 1983). In a population-based study, Furlan and colleagues have shown that in a 32-year period (1945 to 1976) the incidence of ICH was significantly less in the latter part of this period (13.3/100,000 from 1945 to 1960, versus 6.7/100,000 from 1961 to 1976) (Furlan et al., 1979). These figures correlated with a decrease in the prevalence and severity of hypertension in this population. A similar trend correlated with a decrease in the prevalence of hypertension has been reported in a Japanese population (Ueda et al., 1981). The beneficial effects of antihypertensive treatment in reducing the risk of ICH were directly demonstrated in the PROGRESS (Perindopril Protection Against Recurrent Stroke Study) trial (Progress Collaborative Group, 2001). The combination of an ACE inhibitor (perindopril) and a diuretic (indapamide) resulted in a 76% relative risk reduction of ICH in comparison with the placebo-treated group at 4 years follow-up.

As hypertension is the most important risk factor in deep hemispheric ICH (Woo et al., 2002), changes in blood pressure levels would be expected to correlate most closely with incidence of deep ICH. Hypertension has a reported frequency of 50–86% in deep ICH patients in the studies that have specifically examined this subgroup (Brott et al., 1986; Woo et al., 2002; Viswanathan et al., 2006). Other studies have noted a high frequency of left ventricular hypertrophy in autopsy cases of ICH (Mutlu et al., 1963; Brewer et al., 1968; Stebbens, 1972) as well as significantly higher blood pressure reading on admission as compared to other forms of stroke (Ojemann and Heros, 1983). In deep hemispheric ICH, hypertension has been shown to be a risk factor for recurrence in several small studies (Passero et al., 1995; Arakawa et al., 1998).

By contrast, there is substantial evidence that hypertension may not be a predictor of lobar ICH. In one study chronic hypertension was reported in only 31% of cases of lobar ICH (Ropper and Davis, 1980), while in another series only 50% of lobar ICH patients had elevated blood pressure on admission (Kase et al., 1982) and only half of these had previously documented hypertension. In another study (Weisberg, 1979), which compared lobar ICH with deep ICH, only 33% of lobar ICH patients were found to be hypertensive compared to 81% of deep ICH patients.

A recent prospective, population-based case-control study from the Greater Cincinnati metropolitan area of 188 cases of lobar and non-lobar ICH (Woo et al., 2002) found that hypertension was not associated with

increased odds of lobar ICH either in univariate or multivariable models. Similarly, hypertension appears not to affect risk of recurrent ICH among survivors of lobar ICH followed prospectively (O'Donnell et al., 2000; Viswanathan et al., 2006).

38.3.2. Genetic factors

Genetic risk factors for ICH have been implicated by studies showing increased risk conferred by having an affected family member (Alberts et al., 2002; Woo et al., 2002). The only specific genetic risk factor consistently identified has been apolipoprotein E (APOE) genotype as a risk for CAA-related (Greenberg et al., 1996a, 1998; Premkumar et al., 1996; Nicoll et al., 1997) or lobar (Woo et al., 2002) ICH. In a population-based study (Woo et al., 2002), the presence of either APOE ε2 or ε4 alleles increased the risk of lobar ICH (OR 2.3; 95% CI 1.2–4.4). Furthermore, the presence of the ε2 or ε4 alleles of the apolipoprotein E gene is associated with an increased risk of recurrent lobar ICH (28% cumulative recurrence rate at 2 years compared to 10% in lobar ICH patients without either allele) (O'Donnell et al., 2000). The APOE ε2 and ε4 alleles have also been associated with an earlier age of onset of lobar hemorrhage (Greenberg et al., 1996a, 1998).

38.3.3. Dementia

Dementia has generally been considered a major risk factor for CAA-related lobar ICH because of the close molecular relationship between CAA and Alzheimer's disease. Indeed, a pathologic study of 117 brains with Alzheimer's disease demonstrated advanced CAA to be common, with moderate to severe CAA disease in 25.6% of specimens and CAA-related hemorrhages in 5.1% (Ellis et al., 1996). Despite the frequent overlap of Alzheimer's disease with CAA, approximately 60–80% of patients diagnosed with CAA-related ICH do not show clinical symptoms of dementia before their initial hemorrhagic stroke (Mandybur, 1986; Vinters, 1987; Greenberg et al., 1996a). The association of CAA and Alzheimer's disease appears to be due in part to the shared genetic risk factor apolipoprotein E ε4, although as discussed below, there are substantial differences between the roles of APOE in the two disorders. Recent work (Smith et al., 2002) suggests that cognitive impairment prior to lobar ICH is associated with white matter disease, another likely manifestation of CAA.

38.3.4. Other risk factors

Other risk factors for ICH have been examined, including cigarette smoking, alcohol consumption, and serum cholesterol. One study found a 2.5-fold increased risk of intracranial hemorrhage (both ICH and subarachnoid hemorrhage) in cigarette-smoking Hawaiian men of Japanese ancestry (Abbott et al., 1986). A Finnish study, however, did not find cigarette smoking to be an independent risk factor (Juvela et al., 1995). Data from both the Physicians' Health Study and the Women's Health study documented a significant association between cigarette smoking and ICH risk (Kurth et al., 2003a, b). After controlling for several vascular risk factors, smoking greater than 20 cigarettes per day in men was found to be an independent risk factor for ICH (RR 2.06; 95% CI 1.08–3.96). For women similar results were observed for those who smoked more than 15 cigarettes per day (RR 2.67; 95% CI 1.04–6.90).

Alcohol consumption has been independently associated with risk of lobar and deep ICH in several studies (Donahue et al., 1986; Juvela et al., 1995). This effect of alcohol has been shown to be strongly dose-dependent. One study, which analyzed ICH subtypes separately, found that frequent alcohol consumption was independently associated with lobar ICH but not deep ICH (Woo et al., 2002). A similar dose-dependent effect has been documented in alcohol consumption 24 hours and 1 week prior to ICH (Juvela et al., 1995).

Low-serum cholesterol has been found to be associated with ICH in several population-based studies (Tanaka et al., 1982; Iso et al., 1989; Yano et al., 1989; Gatchev et al., 1993; Lindenstrom et al., 1994; Giroud et al., 1995; Iribarren et al., 1996). Low serum cholesterol (< 160 mg/dL) has been shown to be associated with a higher risk of ICH in both Japanese men (Tanaka et al., 1981) and Hawaiian men of Japanese origin (Ueshima et al., 1980). However, other studies have yielded conflicting results (Giroud et al., 1995; Kubota et al., 1997; Thrift et al., 1998; Zodpey et al., 2000). One study which analyzed ICH according to location found low-serum cholesterol to be associated with both lobar and deep ICH (Giroud et al., 1995) while another study which analyzed ICH according to presumed etiology, found low-serum cholesterol to be associated specifically with deep ICH (Segal et al., 1999).

Hematologic abnormalities associated with coagulopathy are important risk factors for ICH, representing approximately 8% of all ICH (Bamford et al., 1988; Gebel et al., 2002a). The most common coagulopathies are iatrogenic (see following section). Other hematologic disorders which may predispose to ICH include congenital and acquired factor deficiency disorders, thrombocytopenic and thrombocytopathic disorders, as well as lymphoproliferative disorders (Hart et al., 1995).

Structural lesions such as ruptured aneurysms, arteriovenous malformations, cavernous angiomas, and tumors contribute to a small proportion of ICH in the literature. Vascular malformations have been reported to cause up to 4–5% of ICH (Furlan et al., 1979; Broderick et al., 1992) and are an important etiology, particularly in younger patients. Structural lesions have been noted to be present in as much as 65% of individuals 45 years old or younger presenting with lobar ICH (Zhu et al., 1997).

Prior ischemic stroke has been shown to be associated with ICH in several studies with relative risks of 5- to 22-fold (Okada et al., 1976; Brott et al., 1986; Woo et al., 2002). In the Greater Cincinnati study, prior stroke was an independent risk factor, associated with a 13-fold increased risk of deep ICH and 4.1-fold risk of lobar ICH in multivariable analysis (Woo et al., 2002). ICH occurring well after previous ischemic stroke appears to be distinct from hemorrhagic transformation of an acute cerebral infarct, a recognized cause of thrombolysis-related ICH in both stroke and acute myocardial infarction (Sloan et al., 1995). Risk factors for spontaneous ICH are summarized in Table 38.1.

38.3. Iatrogenic causes of intracerebral hemorrhage

38.3.1. Warfarin anticoagulation

Medical therapy with warfarin (Furlan et al., 1979; Wintzen et al., 1984; Albers et al., 1991; Atrial Fibrillation Investigators, 1994; Hart et al., 1995) is associated with a 6- to 11-fold increase in relative risk of ICH. Warfarin-related ICH is associated not only with increased risk of ICH, but also with increased severity of hemorrhage, approximately doubling its mortality (Radberg et al., 1991; Hart et al., 1995; Rosand et al., 2004b). The absolute risk of ICH related to warfarin has been reported to range from 0.3–1.7% per year (Hart et al., 1995). Risk is higher in those with concomitant hypertension (Barron and Fergusson, 1959; Wintzen et al., 1984; Kase et al., 1985; Dawson et al., 1993; Hylek and Singer, 1994; Smith et al., 2002), older patients (> 70 years) (Landefeld and Goldman, 1989; Hylek and Singer, 1994), and those on combined therapy with aspirin. Aspirin and warfarin therapy together approximately double the risk of ICH compared to warfarin alone (Hart and Pearce, 1993; Hart et al., 1995). Risk of anticoagulation-related ICH may be highest during the early period after initiation (Kase et al., 1985; Radberg et al., 1991). A substantial subset of warfarin-related ICH may reflect underlying CAA (Rosand, 2000).

Excessive anticoagulation is a well-established risk factor for ICH (Barron and Fergusson, 1959; Snyder and Renaudin, 1977; Wintzen et al., 1984; Kase et al., 1985; Landefeld and Goldman, 1989; Hylek and Singer, 1994; NINDS t-PA Stroke Study Group, 1997; Smith et al., 2002). Recent work has shown that risk of ICH doubles with every 0.5-point increase in prothrombin time above 2.0 (Hylek and Singer, 1994).

Another emerging risk for warfarin-related ICH is the extent of white matter damage. In the Stroke Prevention in Reversible Ischemia (SPIRIT) study, investigators found that severe and confluent white matter damage was associated with a hazard ratio for ICH of 9.2 in patients with post-ischemic stroke (SPIRIT investigators, 1997). Similarly, a case-control study of consecutive patients found white matter damage to be an independent (multivariable adjusted OR 12.9, 95% CI 2.8–59.8) and dose-dependent risk factor for warfarin-related hemorrhage (Smith et al., 2002).

Anticoagulation-related hemorrhages may progress more slowly (as long as 48–72 hours) and are associated with significantly higher mortality (Radberg et al., 1991; Hart et al., 1995; Rosand et al., 2004b) relative to non-warfarin ICH. Decision analysis models suggest that because of the substantial risk of recurrence following lobar ICH (see above) and the poor outcome associated with warfarin-related ICHs, anticoagulation should be withheld in patients with previous lobar ICH (Eckman et al., 2003).

38.3.2. Heparin

Intracerebral hemorrhage related to heparin therapy most commonly occurs in the setting of anticoagulation in acute ischemic stroke and is exceedingly rare in other cases of heparin therapy for non-cerebrovascular etiologies (Drapkin and Merskey, 1972; Handley et al., 1972). Ischemic tissue from acute or recent embolic infarction usually occurs within 24–48 hours of the start of therapy (Camerlingo et al., 1994) and elevated partial prothrombin time

Table 38.1

Risk factors for lobar and deep ICH

Risk factors for deep ICH	Risk factors for lobar ICH
Hypertension	Advanced age
Prior ischemic stroke	APOE ε2 or ε4
Frequent use of alcohol	Alzheimer's disease
Family history of ICH	Family history of ICH
Cigarette smoking	Frequent use of alcohol
Low-serum cholesterol	Previous ischemic stroke
	Low-serum cholesterol

(PTT) is common (Babikian et al., 1989; Chamorro et al., 1995). In addition, uncontrolled hypertension has been shown to be a risk factor (Cerebral Embolism Study Group, 1984). Current recommendations therefore dictate strict control of blood pressure (< 180/100 mmHg) as well as close monitoring of PTT (1.5 times the control value) if acute heparin therapy is used in embolic infarction (Chamorro et al., 1995).

38.3.3. Fibrinolytic agents

Fibrinolytic agents such as tissue-type plasminogen activator (tPA) are commonly used in acute coronary syndromes and acute ischemic stroke, as well as pulmonary venous thrombosis and thrombosis of the limbs. A major but infrequent complication of this therapy is ICH, which has been reported in 0.4–1.3% of patients with acute myocardial infarction treated with alteplase (TIMI Study Group, 1989). Hemorrhages tend to occur acutely with 40% occurring during the infusion and an additional 25% within 24 hours of the start of treatment (Gore et al., 1991). The majority (70–90%) of these hemorrhages are lobar and some are multifocal (Kase et al., 1990). Multifocal ICH is associated with increased mortality (Kase et al., 1990, 1992; Gore et al., 1991; Sloan et al., 1995). The mechanism of hemorrhage in these cases remains unclear. Advanced age, history of hypertension, and aspirin use prior to therapy, have been suggested as possible risk factors although compelling evidence is lacking (Kase et al., 2004). Underlying small-vessel pathology may contribute to hemorrhage in select populations, as existing CAA has been shown to be associated with increased ICH rates in several studies (Pendlebury et al., 1991; Wijdicks and Jack, 1993; Sloan et al., 1995).

The use of thrombolytic agents in acute ischemic stroke has also been associated with ICH. The National Institute of Neurological Diseases and Stroke (NINDS) rt-PA Stroke Study (NINDS and Stroke rt-PA Stroke Study Group, 1995b) demonstrated improved outcome in patients treated with alteplase despite a ten-fold increase in symptomatic ICH during the first 36 hours (6.4% versus 0.6%). Hemorrhage occurred in both lobar and deep hemispheric regions and was associated with a 45% mortality rate (Clark et al., 1997). Trials of intravenous streptokinase have shown significantly higher rates of ICH ranging from 6% to 21% with high mortality (Donnan et al., 1995; Multicentre Acute Stroke Trial—Italy [MAST-I] Group, 1995; Multicenter Acute Stroke Trial—Europe Study Group, 1996). This may be due to an inappropriately high dose of drugs for cerebrovascular disease or the longer-lasting fibrinolytic effect of streptokinase compared with tPA (Clark et al., 1997). Although a precise mechanism is not defined, the elevated rates of ICH in cerebrovascular therapy as compared with other therapeutic indications suggests that underlying cerebral ischemia or infarction does play an important role in the development of hemorrhage. Hyperglycemia has been found to be a contributing risk factor for hemorrhage in cerebrovascular IV tPA treatment (Bruno et al., 2002).

38.3.4. Antiplatelet agents

The role of antiplatelet use in the risk of ICH is controversial. Pooled evidence from large randomized trials of ICH-free populations suggests that there is a small but significant increased risk of intracranial hemorrhage in aspirin users, with an absolute excess incidence of approximately 1 per 10,000 patient-years (He et al., 1998; Antithrombotic Trialists' Collaboration, 2002). However, elevated risk of ICH was not seen in association with various doses of aspirin in several secondary ischemic stroke prevention trials (Canadian Cooperative Study Group, 1978; Bousser et al., 1983; American–Canadian Co-Operative Study Group, 1985; UK-TIA Study Group, 1988) including the European Stroke Prevention Study (ESPS Group, 1987; Diener et al., 1996). Similarly, patients who continue on antiplatelet treatment following lobar or deep ICH do not demonstrate a major increase in risk of recurrent hemorrhage (Viswanathan et al., 2006).

38.3.5. Other drugs associated with ICH

Drug-related ICH is an important cause of nontraumatic parenchymal hemorrhage particularly in younger patients (Broderick et al., 1992; Woo and Broderick, 2002). Specifically, cocaine and amphetamine have been implicated. Cocaine-related ICH is thought to result from a sudden increase in blood pressure associated with its use. Cocaine-related vasculitis or vasculopathy is rare (Levine et al., 1990; Peterson et al., 1991; Aggarwal et al., 1996; Nolte et al., 1996). Recently, the prescription medication phenylpropanolamine was found to be associated with increased risk of ICH in a case-control study (Kernan et al., 2000) after several previous reports in the literature (Kikta et al., 1985; Lake et al., 1990).

38.4. Pathophysiologic features

38.4.1. Deep hemispheric intracerebral hemorrhage

Spontaneous ICH most commonly occurs in the basal ganglia, cerebral hemispheres, thalamus, brainstem and cerebellum (Fisher, 1961b; Walshe et al., 1977;

Mohr et al., 1978; Wiggins et al., 1978; Furlan et al., 1979; Kase et al., 1982; Kunitz et al., 1984). These areas are supplied by perforating arteries that arise from the large basal cerebral arteries. It is thought that these arteries are more directly exposed to the effects of high blood pressure because of the lack of gradual decrease in vessel caliber as in other areas of the cerebrovascular circulation (Garcia and Ho, 1992). Long-standing hypertension causes a series of pathologic changes that lead to segmental constriction of these blood vessels, termed lipohyalinosis by C.M. Fisher (1971).

Lipohyalinosis is defined by segmentally occurring hyalinization and fibrinoid changes in the vessel wall of small penetrating arteries (< 200 μm in diameter) (Fisher, 1971; Garcia and Ho, 1992) (Fig. 38.2). This leads to the development of non-compliant, narrowed vessels that are susceptible to both sudden closure (causing lacunar infarction) or rupture (resulting in ICH). The exact mechanism which results in rupture has not been conclusively demonstrated. Cerebral microaneurysms (Charcot and Bouchard, 1868; Fisher, 1972), once thought to represent the major mechanism of rupture, are only described in a small number of patients. Hemorrhagic expansion of fibrin or bleeding globules of tissue have been described, but are thought to be associated only with ICH secondary to sudden elevations in blood pressure (Garcia and Ho, 1992; Manno et al., 2005).

It is currently thought that the initial hemorrhage dissects along white matter tissue planes, thus encircling areas of intact neural tissue (Manno et al., 2005). Neurologic deterioration may result from development of cerebral edema, which commonly appears within hours because of clotting of the hematoma, consumption of plasma clotting factors, and release of plasma proteins into the surrounding white matter (Gebel et al., 2002a; Xi et al., 2002). Numerous experimental models have supported this model (Lee et al., 1995, 1996a, b, 1997a, b; Wagner et al., 1996; Xi et al., 1998, 2001b, 2002). Peak edema occurs 3–7 days after ICH and corresponds with the lysis of red blood cells (Xi et al., 2002). Direct neural toxicity due to hemoglobin and hemoglobin degradation products also occurs (Xi et al., 2001a, 2002). Retrospective evidence suggests that patients with larger relative amounts of cerebral edema compared with hematoma volume have worse clinical outcomes (Gebel et al., 2002a).

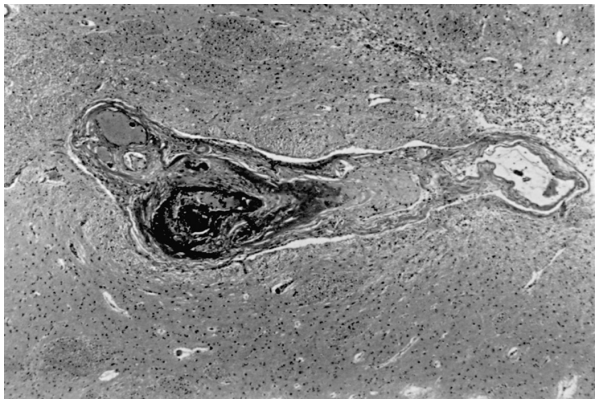

Fig. 38.2. Terminal segment of a lenticulostriate artery showing marked mural changes (hyalinization and fibrinoid change) as well as occlusion of the lumen. (H&E × 60). Reprinted from Marti-Vilalta et al. (2004) with permission from Elsevier.

The role of cerebral ischemia in ICH is less clear. Cerebral blood flow studies have described an area of possible decreased perfusion surrounding the cerebral hemorrhage (Mayer et al., 1998; Siddique et al., 2000; Kidwell et al., 2001; Rosand et al., 2002). In addition, glutamate and other excitotoxins have been reported to be increased in perihematomal tissue (Castillo et al., 2002; Qureshi et al., 2003) as well as DNA markers of cellular injury and apoptosis (Hickenbottom et al., 1999; Qureshi et al., 2001). However, PET studies have demonstrated normal oxygen extraction ratio in the perihematomal region suggesting hypoperfusion may be due to decreased metabolism and not cerebral ischemia (Zazulia et al., 2001).

38.4.2. Lobar intracerebral hemorrhage

Lobar hemorrhages occur in the subcortical white matter, extending longitudinally in a plane parallel to the cortex. Lobar ICH can occur in all lobes but is predominantly found in the posterior regions, namely the parietal, temporal, and occipital lobes (Ropper and Davis, 1980; Kase et al., 1982) (Table 38.1). The posterior predominance of hemorrhage is not explained by relative lobe size as the 3:1 ratio between parietotemporo-occipital and frontal hematomas exceeds the volumetric ratio (2:1 or 3:2) between these regions (Kase et al., 1982). In addition, microhemorrhages in patients with lobar ICH tend to occur more frequently in the temporal and occipital lobes compared to other hemispheric regions ($p < 0.0001$) (Rosand et al., 2005).

Prior to the routine clinical use of gradient-echo or T2*-weighted MRI techniques, the etiology of a substantial proportion of lobar ICH remained unidentified (Kase et al., 1982). More recent data using these techniques (Greenberg, 1998) has allowed for increased recognition of CAA as a common underlying etiology for lobar ICH. Although most pathologic occurrences of CAA do not lead to vessel rupture and ICH, this

entity nonetheless accounts for a substantial proportion of all spontaneous lobar ICH in elderly patients. Estimated rates of 11–15% emerged from autopsies of elderly patients with ICH (age $\geq$ 60 years) at the Japanese Yokufukai Geriatric Hospital between 1979 and 1990 (Itoh et al., 1993) and the Hawaiian Kuakini Hospital between 1965 and 1976 (Lee and Stemmermann, 1978). Analysis of consecutively encountered clinical patients at Massachusetts General Hospital suggests an even greater proportion of hemorrhages, approximately 34%, attributable to CAA (Greenberg et al., 1998; O'Donnell et al., 2000; Knudsen et al., 2001) (Table 38.2). The apparently higher frequency of CAA in the MGH cohort might reflect either a lower incidence of hypertensive ICH in this population or secular improvements in blood pressure control as well as the methodological differences between autopsy-based and clinic-based studies.

In order to identify those lobar ICHs caused by CAA, a set of criteria termed the "Boston criteria" (Knudsen et al., 2001) have been established. The presence of multiple, strictly lobar hemorrhages detected by gradient-echo MRI sequences is highly specific for severe CAA in elderly patients with no other definite cause of ICH such as trauma, ischemic stroke, tumor, coagulopathy, or excessive anticoagulation (*probable* CAA-related ICH) (Greenberg et al., 1999; Knudsen et al., 2001). In a series of 50 patients identified with probable CAA, APOE allele frequencies were comparable to 68 previously published cases (Greenberg et al., 1998) with pathologically demonstrable CAA (Greenberg, 1998) (Table 38.3). High specificity for the diagnosis of CAA is also seen when the Boston criteria are compared against the established gold standard of histologic examination of specimens from autopsy, hematoma evacuation or cortical biopsy (Knudsen et al., 2001) (Table 38.4). To date, of the 45 cases of lobar ICH diagnosed on clinical and radiologic grounds, all 19 cases with probable CAA also had a pathological diagnosis of CAA. Sixteen of the 26 cases with only a single lobar ICH (*possible* CAA-related ICH) had a pathological diagnosis of CAA. The estimated proportion of primary lobar ICH in the elderly caused by CAA using this method is 74% (Knudsen et al., 2001).

Examination of the clinical characteristics that predispose to CAA-related ICH (Table 38.1) suggests that its incidence is likely to rise with the aging of the population and is unlikely to be reduced through control of modifiable risk factors. Advancing age is the strongest clinical risk factor for CAA-related hemorrhage, as predicted by the age dependence of the underlying pathology (Tomonaga, 1981; Vinters and Gilbert, 1983; Masuda et al., 1988; Greenberg and Vonsattel, 1997). All 26 patients identified with CAA-related ICH in three large autopsy series were older than 60 years, and 23 of 26 (88%) older than 70 years (Jellinger, 1977; Lee and Stemmermann, 1978; Itoh et al., 1993). A similar pattern was observed among consecutive patients diagnosed radiologically at Massachusetts General Hospital and analyzed for age at first-CAA-related ICH, though with slightly younger age distribution as expected in a clinically based series. Among 105 patients diagnosed with CAA between July 1994 and October 2001, first-ICH

Table 38.2

Estimated prevalence of CAA-related ICH in a clinical series of elderly patients

ICH location	Percentage of total*
Lobar	45.9 × 74%† = 34% of all primary ICH in elderly due to CAA
Deep hemispheric	41.1%
Brainstem	3.7
Cerebellum	8.5
Intraventricular	0.9

*Data from 355 consecutive patients aged $\geq$ 55 presenting to Massachusetts General Hospital with spontaneous ICH.
†The estimated proportion of primary lobar ICH in the elderly caused by CAA, based on detection of advanced CAA in 29 of 39 consecutive pathology specimens of lobar ICH (Knudsen et al., 2001).

Table 38.3

Apolipoprotein E (ApoE) allele. Frequency in probable CAA versus pathologically proven CAA

Diagnosis	ApoE allele frequency	
	ε2	ε4
Probable CAA	0.18	0.20
Definite CAA*	0.17	0.26

*Confirmed by pathology.

Table 38.4

Clinical–pathologic correlation of diagnosis of CAA by Boston criteria

Clinical diagnosis	*n*	Pathological diagnosis	
		CAA present	CAA absent
Probable CAA	19	19	0
Possible CAA	26	16	10
Total	45	35	10

occurred at a mean age of 76.1 ± 8.3 years (range 53–92 years). Ninety-seven percent of patients were older than 60 years at first hemorrhage, 75% older than 70 years, 39% older than 80 years, and 4% (4 of 105 patients) in their 90s. There is no marked predilection for gender either in the Massachusetts General Hospital clinical series (54% men, 46% women) or in pathologic cases (49% men, 51% women) (Vinters, 1987).

CAA appears on pathologic analysis as a variable combination of vascular amyloid deposition and vessel breakdown (Fig. 38.3). Affected vessels are the capillaries, arterioles, and small- and medium-sized arteries primarily of the cerebral cortex, overlying leptomeninges, and cerebellum, with the white matter and deep gray structures largely spared. The distribution of CAA is typically patchy and segmental, such that heavily involved vessel segments may alternate with essentially amyloid-free regions (Fig. 38.3C). In its mildest detectable form, congophilic material accumulates at the border of the vessel's media and adventitia (Fig. 38.3A). Amyloid-lined vacuoles often seen at this stage (Vonsattel et al., 1991) may represent former sites of vascular smooth muscle cells that have died in apparent response to the surrounding amyloid. In moderately severe segments of CAA, vascular amyloid extends throughout the media to replace essentially the entire smooth muscle cell layer (Fig. 38.3B).

The most advanced extent of CAA is marked not only by severe amyloid deposition but also by pathologic changes in the amyloid-laden vessel wall. These vasculopathic changes can include microaneurysms, concentric splitting of the vessel wall (Fig. 38.3D), chronic perivascular or transmural inflammation, and fibrinoid necrosis (Fig. 38.3E) (Mandybur, 1986; Vonsattel et al., 1991; Yamada et al., 1996; Maat-Schieman et al., 1997; Uchihara et al., 1997; Vinters et al., 1998). CAA-related vasculopathic changes are often associated with ongoing leakage of blood. It is this combination of extensive amyloid deposition and breakdown of the amyloid-laden vessel walls that appears to act as the substrate for symptomatic hemorrhagic strokes (Mandybur, 1986; Vonsattel et al., 1991; Maeda et al., 1993; Natte et al., 1998; McCarron et al., 1999).

The principal constituent of both vascular amyloid in CAA and plaque amyloid in Alzheimer's disease is the β-amyloid peptide (Aβ). The Aβ peptides are 39- to 43-amino acid proteolytic fragments of the 695- to 770-residue β-amyloid precursor protein (APP). The subset of Aβ peptides with carboxyl terminal extending to position 42 or 43 (denoted as Aβ42) appears to be an important trigger for amyloid aggregation in both vessels and plaques (Jarrett et al., 1993). In support of Aβ42 deposition as an early step in initiation of CAA is the observation that mildly affected vessels can stain positive for Aβ42 but negative for the more common Aβ fragments terminating at position 39 or 40 (Aβ40) (Shinkai et al., 1995; Natte et al., 1999). However, it is Aβ40 that appears to be the predominant species in more heavily involved vessel segments (Iwatsubo et al., 1994, 1995; Mak et al., 1994; Gravina et al., 1995; Castano et al., 1996; Lemere et al., 1996; Mann et al., 1996; Alonzo et al., 1998). Quantitative analysis of brain with mild and severe CAA suggests a progressive addition of Aβ40 to previously seeded vessel segments (Alonzo et al., 1998). A variety of other proteins or protein fragments can also be detected as components of vascular amyloid, though without a known pathogenic role in the breakdown of the vessel wall. These CAA-associated proteins include apolipoprotein E, cystatin C, alpha-synuclein, heparan sulfate proteoglycan, amyloid P component, and several complement proteins (Snow et al., 1990; Vinters et al., 1990; Namba et al., 1991; Kalaria and Kroon, 1992; Ueda et al., 1993; Verbeek et al., 1997; Cho et al., 2001).

Finally, the relationship of the pathology of CAA and APOE genotype provides insight on the importance of both Aβ deposition and vessel breakdown to the pathogenesis of CAA-related lobar ICH. The APOE ε2 and ε4 alleles, each a suggested risk factor for CAA-related ICH (O'Donnell et al., 2000), appear to act at these two distinct stages of CAA to promote hemorrhage. APOE ε4 associates in a dose-dependent manner with increased deposition of Aβ in cerebral blood vessels and neuritic plaques (Schmechel et al., 1993; Greenberg et al., 1995; Olichney et al., 1996; Premkumar et al., 1996). Interestingly however, APOE ε2 appears to promote CAA-related vasculopathic changes such as concentric vessel splitting and fibrinoid necrosis (Greenberg et al., 1998; McCarron et al., 1999). The mechanism of this process is unknown. The domain of the apolipoprotein E protein containing the ε2 determinant is present in both vessel and plaque amyloid deposits (Cho et al., 2001) but has not been linked to any specific pathogenic function.

38.5. Clinical features and diagnosis

All forms of ICH have a similar clinical presentation which results from accumulation of blood in brain parenchyma. There is acute onset of focal neurologic symptoms and patients can also have symptoms commonly associated with increased intracranial pressure (ICP) such as headaches, seizures, or a depressed level of consciousness. Decreased alertness has been reported to represent 60% of the cases (Hier et al., 1977; Mohr et al., 1978) two-thirds of which

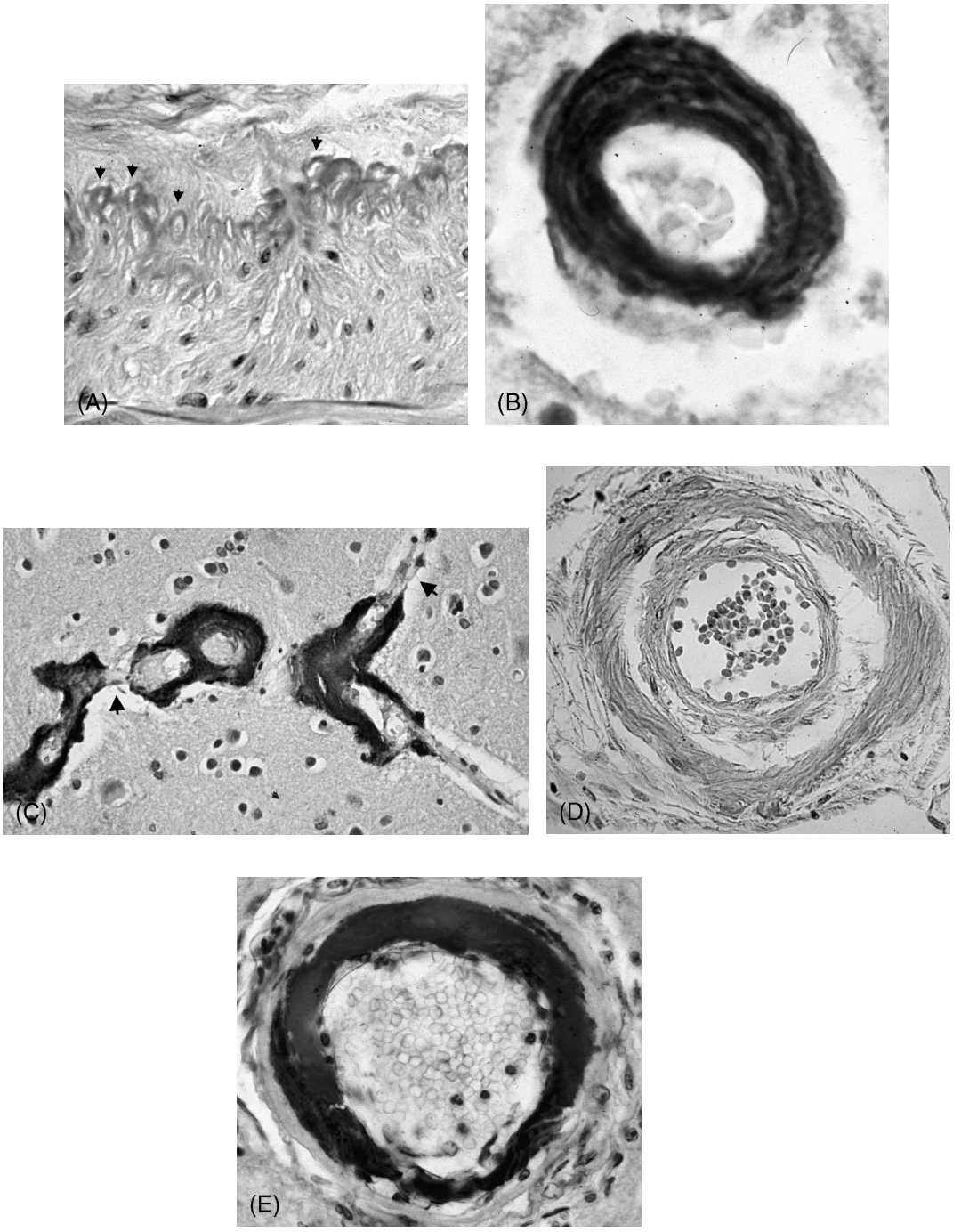

Fig. 38.3. Pathologic appearances of cerebral amyloid angiopathy (CAA). (A) Vessel in longitudinal section. In mild stages of disease, amyloid appears at the outer edge of the vessel media, creating vesicle-like structures (arrows) at site believed to be previously occupied by smooth muscle cells. (B) Further amyloid deposition replaces the media and all smooth muscle cells. (C) Specimen taken from a brain with Iowa APP mutation. Amyloid deposits can cause marked thickening of vessel wall segments that alternate with skipped areas of normal caliber (arrows). (D) Further vasculopathic changes in amyloid-laden vessels include concentric splitting of the vessel wall, creating a vessel-in-vessel appearance. (E) Fibrinoid necrosis signifying entry of plasma components into the wall. Reprinted from Greenberg, 2004 with permission from Elsevier.

can be characterized as coma (Mohr et al., 1978; Wiggins et al., 1978). Patients presenting with coma have been noted to have either large hematomas (Hier et al., 1977) or ventricular extension (Wiggins et al., 1978; Tanaka et al., 1999). Although headache and vomiting are classically reported with ICH, these symptoms may be present in only a minority of patients (Aring, 1964; Mohr et al., 1978). Therefore the absence of these symptoms does not rule out the diagnosis.

Seizures are more common in lobar than deep ICH (Aring, 1964; Mohr et al., 1978; Furlan et al., 1979), occurring in up to 32–35% of cases (Kase et al., 1982; Vespa et al., 2003) presumably because of cortical irritation from the hematoma. However, recent work using continuous EEG monitoring (Vespa et al., 2003) has shown that the rate of seizure in deep ICH may be higher than previously thought.

As for the clinical course of neurologic symptoms in ICH, there was gradual smooth progression of symptoms in two-thirds of the 70 cases in the Harvard Cooperative Stroke Registry, the remaining third with maximal deficit at onset (Mohr et al., 1978). There was no decrease of deficit in any of the cases in the acute phase, consistent with previous clinical observations that improvement in the stroke syndrome rules out ICH (Ojemann and Mohr, 1976). It has been noted in previous clinical series that ICH typically occurs during activity (Fisher et al., 1965; Fisher, 1971). Indeed, it is rare that ICH occurs during sleep (Fisher, 1961a), seen in only 3% of ICH cases in the NINDS Data Bank (Kunitz et al., 1984).

The general physical examination at presentation often reveals hypertension, having been reported as high as 91% in one case series (Mohr et al., 1978). Neurological findings in individual cases allow for localization of the hemorrhage. Putaminal hemorrhages which represent the most common type of deep hemispheric ICH (30–50% of cases) (Fisher, 1961b; Mohr et al., 1978; Wiggins et al., 1978; Furlan et al., 1979; Kase et al., 1982; Kunitz et al., 1984), typically present with hemiplegia, forced eye-gaze deviation, and hemisensory loss with a homonymous hemianopia (Fisher, 1961a; Ojemann and Mohr, 1976; Kase et al., 2004). Pupillary size is normal unless there is uncal herniation, where ipsilateral third nerve palsies can be seen (Fisher, 1961a).

Thalamic hemorrhages account for 10–15% of ICH (Fisher, 1961b; Freytag, 1968; Walshe et al., 1977; Mohr et al., 1978; Wiggins et al., 1978; Furlan et al., 1979; Kase et al., 1982; Kunitz et al., 1984). Virtually all patients present with hemiplegia or hemiparesis and a hemisensory syndrome involving loss of sensation to all modalities of the face, arm and leg (Walshe et al., 1977; Barraquer-Bordas et al., 1981; Kase et al., 2004). The characteristic oculomotor findings in thalamic hemorrhage are upgaze palsy with miotic and unreactive pupils (Fisher, 1959; Walshe et al., 1977; Kase et al., 2004). There may be some signs of Parinaud's syndrome if there is mass effect from the hematoma on the rostral midbrain. There may be downward gaze deviation associated with convergence which gives the appearance that the patient is looking at the tip of the nose (Fisher, 1959; Kase et al., 2004). Rarely, in small thalamic hematomas of the dominant hemispheric, a distinctive aphasia can be seen characterized by fluent speech with poor naming and intact repetition (Mohr et al., 1975; Kase et al., 2004) which may be mistaken for delirium.

The clinical features of cerebellar hemorrhage were initially described in 1959 (Fisher, 1971). These hemorrhages represent 5–15% of hemorrhages in the brain (Fisher, 1961b; Kase et al., 2004). Patients commonly have symptoms that include headache, vomiting, dizziness, and an inability to stand or walk (Kase et al., 2004). Principal features on examination include truncal and appendicular ataxia, ipsilateral gaze palsy typically without hemiplegia (Ott et al., 1974). Other common findings include peripheral facial palsy, nystagmus, and ocular skew deviation. As surgical decompression can be lifesaving in hematomas of larger size, prompt diagnosis is vital.

The clinical course in cerebellar hemorrhage has proven quite unpredictable. Patients can deteriorate to coma quickly and often without warning. Of those patients who were not comatose on admission, 20% did not worsen while 80% deteriorated to coma, one-quarter in the initial 3 hours after presentation (Ott et al., 1974). Work regarding management strategies has focused on identifying predictors of neurologic deterioration. Independent predictors include vermian location of ICH, hydrocephalus, and mass effect on the fourth ventricle (St Louis et al., 1998; Kirollos et al., 2001). Predictors of poor outcome include systolic blood pressure greater than 200 mmHg, hematoma diameter greater than 3 cm, Glasgow coma scale less than 8, acute hydrocephalus, and intraventricular hemorrhage (St Louis et al., 2000). However, the true importance of cerebellar hematoma size as it relates to clinical course remains in question as others have shown that 60% of patients with hematomas greater than 3 cm did not require surgical evacuation (Kirollos et al., 2001).

In lobar hemorrhage, patients present with an acute onset of neurologic symptoms and a variable combination of headache, seizures, and decreased consciousness according to hemorrhage size and location. There is a higher frequency of headache and seizures in these

patients compared to all other forms of ICH and a smaller percentage of presentations with coma (Mohr et al., 1978; Ropper and Davis, 1980; Kase et al., 1982; Weisberg, 1985; Bogousslavsky et al., 1988; Massaro et al., 1991). Common neurologic signs include hemiparesis and visual field defects (Kase et al., 1982).

Pontine hemorrhages carry a grave prognosis, the majority of patients presenting in coma and 78% proceeding to death within 48 hours (Dinsdale, 1964; Kase et al., 2004). Pontine ICH commonly arises from rupture of a distal branch of the paramedian perforator at the junction of the tegmentum and basis pontis. Expansion results in cranial nerve involvement, long tract signs (often quadriplegia), autonomic dysfunction and decreased consciousness. Respiratory dysfunction also occurs resulting in apneustic breathing patterns or less commonly Cheyne–Stokes respiration (Kase et al., 2004). The oculomotor findings include miotic pinpoint pupils (most likely due to interruption of sympathetic fibers), lack of horizontal eye movements, and ocular bobbing. Ocular bobbing refers to brisk conjugate downward eye movement followed by slow return to midposition (Fisher, 1964). It can also occur in pontine infarction or cerebellar hemorrhage (Fisher, 1964; Susac et al., 1970; Ott et al., 1974).

Diagnosis of ICH has become much easier with the advent of modern imaging techniques. CT scan is a rapid and highly sensitive method to assess for acute hemorrhage. Recent work has demonstrated that MRI with gradient-echo sequences may be as reliable as CT in diagnosis of acute ICH (Linfante et al., 1999; Kidwell et al., 2004). This sequence enhances signal dropout associated with deposited hemosiderin (Atlas et al., 1988; Greenberg et al., 1996b; Fazekas et al., 1999; Tsushima et al., 2000). In addition, MRI gradient-echo sequences are useful for detecting small lobar hemorrhages which may remain clinically silent. By detecting old hemorrhagic lesions, gradient-echo MRI provides a clinical method for demonstrating an individual's lifetime history of hemorrhage. This is particularly important in multiple lobar hemorrhage characteristic of CAA (Greenberg et al., 1999) but has also been used to visualize microhemorrhages in other forms of ICH (Roob et al., 2000).

38.6. Treatment

The general approach to therapy of ICH is based on the American Heart Association Stroke Council (Broderick et al., 1999). The management strategy does not differ between lobar ICH and deep hemispheric ICH. Despite the differences in vascular pathology among ICH subtypes, the acute behavior of lobar hemorrhages due to CAA does not appear to differ from the other types of ICH with regard to factors such as mass effect and hematoma expansion (Brott et al., 1997). In addition, response to medical and surgical therapy seems to be similar among different ICH subtypes (Greene et al., 1990; Leblanc et al., 1991; Matkovic et al., 1991; Kase, 1994; Minakawa et al., 1995; Izumihara et al., 1999).

38.6.1. Initial therapy

Evaluation should include a thorough and accurate clinical history as well as documentation of previous medical conditions to discern the etiology of hemorrhage. History of hypertension, previous hemorrhage, cognitive impairment, drug use, or known structural lesions may all be important. Left ventricular hypertrophy (as seen on EKG or chest radiography) can aid in diagnosis of hypertension (Mutlu et al., 1963; Brewer et al., 1968; Stebbens, 1972).

The patient's level of consciousness should be monitored closely as acute neurologic worsening can result from hematoma expansion or rupture into the ventricular system. In those patients with impaired level of consciousness, endotracheal intubation should be considered in those with absent gag reflex and cough, as inadequate clearance of secretions is associated with an increased risk of aspiration pneumonia (Marshall et al., 1983; Coplin et al., 2000). In addition, intubation should also be considered for those patients with decreasing level of consciousness or new brainstem signs. Hypoxia as indicated by $PaO_2 < 60$ or $PaCO_2 > 50$ is an indication for intubation.

There has been controversy regarding blood pressure management in acute ICH. It is argued that rapid lowering of blood pressure may result in a decrease in cerebral perfusion due to a shift in the cerebral autoregulation curve (Gebel and Broderick, 2000). On the other hand, inadequate control of blood pressure could in theory increase hematoma volume during the acute phase of ICH.

Two retrospective studies (Kazui et al., 1996; Fujii et al., 1998) and one prospective study (Brott et al., 1997) have examined hematoma expansion in patients with ICH. In a study of 627 patients with predominantly deep ICH (only 9.7% lobar ICH) (Fujii et al., 1998), multivariable analysis revealed that hematoma expansion was associated with time of symptom onset to imaging, heavy alcohol consumption, hematoma shape, decreased level of consciousness, and serum fibrinogen level. Similarly, another study (Kazui et al., 1996) found that hematoma expansion was more common in those imaged soonest after onset. In a prospective study of 103 patients, hematoma expansion

was seen in 26% of patients within the first hour of imaging (Brott et al., 1997). Based on the evidence from these studies, it is likely that hematoma expansion occurs most often in the initial hours after ICH and with significantly decreased frequency after 24 hours.

These studies did not find an association between blood pressure and hematoma expansion (Kazui et al., 1996; Brott et al., 1997; Fujii et al., 1998); however, methodological problems may confound the strength of this observation. In the study by Brott and colleagues, there was non-standardized use of antihypertensive therapy in select patients as well as surgical hematoma evacuation. The study by Fujii et al. had a more standardized treatment protocol for blood pressure, where target systolic pressure was 150 mmHg or less in all admitted patients. This study found a linear relationship between hematoma growth and elevated blood pressure in univariate analysis (145 mmHg, 6.5%; 145–160 mmHg, 13%; 160–175 mmHg, 14%; > 175 mmHg, 21.7%). However, this association was not seen in subsequent multivariable analysis. Finally, in a recent retrospective study, rate of blood pressure decline within the first 24 hours of presentation was associated with increased mortality (Qureshi et al., 1999a).

Other evidence suggests that modest blood pressure control may be safe. In animal experiments, investigators have shown no difference in perihematomal blood flow between dogs treated with blood pressure lowering agents compared with controls (Qureshi et al., 1999b). In a small randomized study of 14 patients, regional cerebral blood flow as measured by PET scanning were not significantly different in patients with mean arterial pressure greater than 120 mmHg compared to those subjects treated by 15% reduction of blood pressure (Powers et al., 2001).

It is clear that randomized controlled trials are needed to define the role of antihypertensive therapy in acute ICH. In the absence of such conclusive data, the current guidelines have recommended maintaining blood pressure below a mean arterial pressure of 130 mmHg in patients with history of hypertension (Broderick et al., 1999). Various classes of antihypertensive agents have been used effectively, including β-blockers (e.g. metoprolol, labetalol), calcium-channel blockers (e.g. nicardipine), and angiotensin-converting enzyme inhibitors (e.g. captopril). These agents offer the theoretical advantage of reducing blood pressure without increasing ICP and thereby minimizing associated drops in cerebral perfusion. Hydralazine may decrease cerebral blood flow; however, this reduction appears not to be clinically important (Manno et al., 2005). Although sodium nitroprusside is an effective blood pressure lowering agent, it may cause cerebral venodilation resulting in increased ICP. Although it has never been shown to be detrimental in neurologic patients, it is generally recommended to avoid this agent in patients with increased ICP. Since ICH-induced hypertension may be transient and self-limited, the use of short-acting agents is recommended. In patients with an ICP monitor, it is recommended that cerebral perfusion pressure (CPP) be kept higher than 70 mmHg. It is further advised that low blood pressures be treated with aggressive fluid resuscitation and consideration of intravenous pressors if this is inadequate.

Anticoagulation-related hemorrhage has been associated with larger ICH volume (Radberg et al., 1991), more frequent hematoma expansion, and worse clinical outcomes (Hart et al., 1995; Flibotte et al., 2004). Hematoma expansion occurs later in the hospital course in warfarin anticoagulated patients compared to non-anticoagulated ICH subjects (median time to detection of expansion 21.4 hours compared to 8.4 hours) (Flibotte et al., 2004). This suggests warfarin-related ICH patients are at risk for prolonged bleeding and indeed may be at risk well beyond 24 hours. Therefore, rapid reversal of anticoagulation with fresh frozen plasma (FFP) and vitamin K is the appropriate immediate therapy (Mayer, 2003). Intravenous vitamin K is the most rapid method of reversal. There is a very small risk of anaphylaxis which may be further reduced by slow infusion of less than 1 mg per minute (Riegert-Johnson and Volcheck, 2002). A small prospective study (Cartmill et al., 2000) and several case reports (Kelley et al., 1982; Yasaka et al., 2003) suggest that prothrombin complex or factor VII concentrate may reverse anticoagulation faster without the significant volume load associated with FFP. Further studies are necessary in this area before definitive recommendations can be made. Heparin anticoagulation should be reversed with protamine. There is limited evidence to guide treatment in fibrinolytic-related ICH. Cryoprecipitate, FFP, fibrinogen, and platelets have all been recommended (Manno et al., 2005).

38.6.2. Medical management

After initial stabilization of the patient, medical therapy should focus on close neurologic monitoring and treatment of increased ICP, and secondary medical complications. Monitoring ideally should be performed in the setting of a neurologic intensive care unit with experienced physicians, nurses, and medical support staff. This offers the possibility of frequent neurologic examinations to assess for worsening, ICP monitoring if needed, minute-to-minute hemodynamic monitoring, and the means to achieve rapid airway control.

Increased ICP caused by hematoma mass effect and perilesional edema is an important issue in the management of ICH. ICP monitoring, although not yet shown to improve outcome in ICH (Bowers and Marshall, 1980; Unwin et al., 1991), is generally recommended for patients with large hemorrhages, hemorrhages with substantial intraventricular extension, and patients with a Glasgow Coma Scale (GCS) score of less than 8 (Diringer, 1993). A variety of methods can be used to lower ICP including osmotic agents, intubation and hyperventilation, and muscle relaxants (Broderick et al., 1999). Hyperventilation, is the most rapid way to lower ICP and has been used to reverse herniation syndromes (Gujjar et al., 1998; Broderick et al., 1999). It causes cerebral vasoconstriction due to changes in CSF hydrogen ion concentrations (Manno et al., 2005), consequently leading to decreased cerebral blood volume (CBV). As the choroid plexus rapidly equilibrates hydrogen ion concentrations, its effects last only several hours (Gress et al., 2003). Reduction of pCO_2 to 30–35 mmHg, achieved by raising the ventilation rate while maintaining constant tidal volume, lowers ICP by 25–30% (level of evidence III–V, grade C recommendation) (Broderick et al., 1999). Osmotic therapeutic agents such as intravenous mannitol, glycerin, or loop diuretics act by removing water from the intracellular and interstitial spaces in brain tissue surrounding the hematoma, thus reducing ICP. There is evidence to suggest that prophylactic scheduled administration of osmotic agents irrespective of ICP does not improve outcome (Yu et al., 1992). A reasonable practice is to employ these agents on an as-needed basis, treating only when there is evidence of increased ICP. Finally, neuromuscular paralytic agents may be used in combination with adequate sedation as this may reduce intrathoracic and jugular venous pressure associated with agitation, coughing, straining, or fighting against the ventilator (level of evidence III–V, grade C recommendation) (Broderick et al., 1999; Gress et al., 2003). Finally, it should be noted that corticosteroids have not been shown to have a beneficial effect on overall outcome (Tellez and Bauer, 1973; Portenoy et al., 1987) and their use has been associated with higher infection rates and hyperglycemia (Portenoy et al., 1987).

Although seizures are relatively frequent in ICH patients (Kase et al., 1982; Vespa et al., 2003) it is unclear whether prophylactic anticonvulsant use improves outcome. A reasonable practice is to avoid prophylactic anticonvulsants and treat seizures symptomatically.

Hyperglycemia and diabetes have been identified as independent risk factors for fatal outcome in ICH (Wong, 1999; Arboix et al., 2000; Passero et al., 2003; Rosand et al., 2004b). Furthermore, observations suggest that hyperglycemia may predispose to increased bleeding (De Courten-Myers et al., 1992; Williams et al., 1998; Demchuk et al., 1999; Meigs et al., 2000; Kase et al., 2001; Bruno et al., 2002; Song et al., 2003). Although unstudied in ICH, aggressive glycemic control in critically ill patients in general have demonstrated improved outcomes (Van den Berghe et al., 2001). It is therefore reasonable practice to treat hyperglycemia aggressively in all ICH patients, with frequent glucose monitoring and subcutaneous insulin therapy or a continuous insulin infusion in difficult to control patients. A randomized clinical trial is needed to define the importance of glucose control in the clinical course and outcome of ICH.

38.6.3. Surgical management

Surgical intervention in ICH has not been shown to improve clinical outcome or survival in lobar (Morgenstern et al., 1998; Zuccarello et al., 1999) or deep hemispheric ICH (Mckissock et al., 1961; Batjer et al., 1990; Morgenstern et al., 2001). Most recently, data from a large randomized controlled trial (Surgical Trial in Intracerebral Haemorrhage, or STICH) comprised of 1,033 patients showed no benefit in outcome or mortality for early surgery versus medical management of primary ICH (Mendelow et al., 2005). In the subgroup analysis, there was a 29% relative benefit for those patients whose hematoma reached 1 cm to the cortical surface; however, this benefit was no longer present after the statistical adjustment for prespecified subgroups. Surgical hematoma evacuation is performed empirically in selected cases, and may be lifesaving in patients with large hematomas, mass effect, and brainstem compression, particularly those who initially present with intact neurologic exam and acutely deteriorate because of mass effect. The preadjusted results of the subgroup analysis in the STICH trial suggest that a selected group of patients may benefit from surgical intervention. Further trials are needed to address this question.

In cerebellar ICH, although there are no randomized controlled trials comparing surgical versus medical therapy, there is a general consensus that hematomas greater than 3–4 cm should be treated surgically, particularly if associated with clinical deterioration or hydrocephalus (Kobayashi et al., 1994; Mathew et al., 1995; Siddique and Mendelow, 2000).

Minimally invasive surgical techniques have been pursued in recent years for evacuation of lobar hematomas (Gebel and Broderick, 2000). A variety of

techniques have been reported including stereotactic removal by cannula, ultrasonic aspiration, and endoscopic evacuation. The results of a randomized trial evaluating endoscopic hematoma evacuation involving 100 patients demonstrated reduced mortality (30% versus 70%, $p < 0.05$) in surgically treated lobar ICH patients compared with medical therapy (Auer et al., 1989). The benefit in this trial seemed limited to larger volume hematomas in the lobar location. There has been recent interest in the technique of instillation of thrombolytic agents in the hematoma bed combined with aspiration, and several studies have demonstrated the feasibility of this approach (Miller et al., 1993; Montes et al., 2000; Rohde et al., 2000; Teernstra et al., 2003). Rebleeding rates with this approach do not seem to be different from rates seen with aspiration alone (mean 4–5%, range 0–16%) (Gebel and Broderick, 2000). A multicenter randomized trial of 71 patients tested whether scheduled instillation of urokinase and clot aspiration was superior to medical therapy. The study demonstrated that there was a reduction in hematoma volume in the surgical group, but no difference in mortality compared to the medically treated group (Teernstra et al., 2003). Further studies are clearly needed to address this question fully.

38.7. Outcome

The overall outcome from ICH is poor and mortality rates have been reported to range from 40% to 50% (Herman et al., 1982; Broderick et al., 1989, 1992, 1993a; Bamford et al., 1990; Giroud et al., 1991; Fogelholm et al., 1992; Broderick, 1993). Univariate (Carlberg et al., 1993), multivariable (Kwak et al., 1983; Tuhrim et al., 1988, 1999; Young et al., 1990; Broderick et al., 1993b; Lisk et al., 1994; Mayer et al., 1994; Diringer et al., 1998; Gebel et al., 2002b), and decision analysis models (Flemming et al., 2001), have been undertaken to define the predictors of poor outcome. These include volume of ICH, age, Glasgow Coma Score on admission, pulse pressure, admission blood pressure, relative edema volume, presence of intraventricular blood and hydrocephalus. Initial hematoma volume seems the most important individual predictor of outcome.

Warfarin-related hemorrhage has been shown to double the risk of mortality in a dose-dependent manner (Radberg et al., 1991; Hart et al., 1995; Rosand et al., 2004a). Predictors of mortality in warfarin-related hemorrhage were age and presence of diabetes (Rosand et al., 2004a). As discussed above, hematoma expansion occurs in warfarin-related hemorrhage and may partially mediate its effect on mortality (Rosand et al., 2004b). Poor outcomes are also associated with the above variables in thrombolysis-associated hemorrhage (Gore et al., 1995; Sloan et al., 1998). Thrombolysis associated hemorrhage also carries a greater risk of mortality and this seems largely due to the greater volume of these hemorrhages (Gebel et al., 1998; Sloan et al., 1998).

In an important study examining physicians' perception of futility of care in ICH, withdrawal of care was found to be the most important predictor of outcome from ICH (Becker et al., 2001). This work suggests that withdrawal of care based on perceived prognosis in ICH may introduce bias in defining predictors of outcome.

38.8. Future directions and research

The current understanding of the pathophysiologic mechanisms of ICH and potential areas of future research were defined in a recent NINDS Workshop on Acute Intracerebral Hemorrhage (NINDS ICH Workshop Participants, 2005). These areas include basic science research on ICH, research in neuroimaging, medical advances and new surgical techniques.

Recent research has focused on formation and natural history of perihematomal edema in ICH which most commonly develops in the first 24–48 hours (Gebel et al., 2002a; Xi et al., 2002). The effect of perihematomal edema on clinical outcome remains unclear. One study suggests that edema may lead to clinical deterioration (Mayer et al., 1994) while another found improved functional outcome in patients with edema (Gebel et al., 2002b). In addition, the significance and effect of late perihematomal edema also remains to be further elucidated. One study found that late edema occurred in 7 of 76 patients and was associated with clinical worsening in 3 patients (Zazulia et al., 1999). The evolution and natural history of perihematoma edema may be studied with serial MRI FLAIR sequences to correlate it with hemorrhage size and location. As experimental models have suggested that perihematomal edema may be mediated through the effect of thrombin and other blood breakdown products on the blood–brain barrier (Lee et al., 1996b; Xi et al., 2001a), correlations between these molecular changes and neuroimaging characteristics may provide a link between the molecular mechanisms, radiographic data, and clinical outcomes. Novel approaches such as using diffusion tensor imaging (DTI) and diffusion spectrum imaging (Kunimatsu et al., 2003; Lin et al., 2003) may shed light onto the effect of hemorrhage and perihematomal edema on local and global neuronal integrity.

Prevention of hematoma expansion is also a key focus of current investigation. Initial interest in

antifibrinolytics has waned after a recent pilot study of epsilon-aminocaproic acid was stopped because it did not show efficacy (Piriyawat et al., 2004). The recombinant activated factor VIIa (rFVIIa) has shown promise as a hemostatic agent in a phase IIB trial where three doses of rFVIIa were administered within 4 hours to three groups of patients presenting with acute ICH and compared to placebo. The recently published results from this study demonstrated that the mean increase in hematoma volume was 29% in the placebo group as compared with 16%, 14%, and 11% in the groups given 40 μg, 80 μg and 160 μg, respectively ($p = 0.01$ for comparison of the three rFVIIa groups versus placebo). The rFVIIa treated patients were less disabled as compared to placebo treated patients ($p = 0.004$) and had lower mortality at 90 days (18% versus 29%; $p = 0.02$). There was an increase in thromboembolic complications (myocardial cerebral infarction) in the rFVIIa patients (7% versus 2%; $p = 0.12$) which will need to be carefully addressed in follow-up studies.

With advances in the understanding of the pathogenesis of ICH, preventive strategies based on the pathophysiologic pathways which lead to hemorrhage will become important. In lobar ICH due to CAA, treatment targets might include the processes of Aβ synthesis, deposition, toxicity, and clearance (Selkoe, 1999), as well as other steps required for vessel breakdown. An example of potential future approaches to prevention of ICH is Cerebril, a glycosaminoglycan mimetic designed to interfere with amyloid fibril formation and recently explored in a phase II study of 24 subjects diagnosed with CAA (Greenberg et al., 2004).

Further improvements in our understanding of the pathophysiologic mechanisms underlying ICH should lead to more effective therapeutic strategies and improved outcomes. A multidisciplinary collaborative approach is likely to yield important insights in the management and treatment of this devastating disease.

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Chapter 39

Subarachnoid hemorrhage

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39.1. Introduction

Subarachnoid hemorrhage (SAH) is defined as bleeding into the subarachnoid space of the brain. The most common etiology of SAH is trauma (Greene et al., 1995, 1996; Taneda et al., 1996; Hanlon et al., 2005). Other etiologies are shown in Table 39.1 and include aneurysmal SAH, perimesencephalic hemorrhage, vertebral artery dissection, and arteriovenous malformations (AVMs) to name a few. Aneurysmal SAH accounts for approximately 85% of all causes of non-traumatic SAH and will be the focus of this chapter. Perimesencephalic SAH, SAH from vertebral artery dissection and traumatic SAH are briefly reviewed. Isolated spinal SAH is not discussed in this chapter.

39.2. Aneurysmal SAH

39.2.1. Introduction

Intracranial aneurysms are uncommon vascular lesions that can cause significant morbidity and mortality if they rupture. This has led to an increased emphasis on early detection and treatment. It is well recognized that most intracranial aneurysms are acquired, and arise spontaneously although in some cases they are secondary to trauma and infection. Also, the natural history of untreated ruptured aneurysms is almost uniformly fatal. Despite advances in both diagnosis and treatment the overall morbidity and mortality remains high.

39.2.2. Epidemiology

The overall prevalence of unruptured aneurysms is the subject of controversy. A single center autopsy study found 84 patients with 102 unruptured aneurysms in a total of 10,259 autopsies, giving a prevalence of 0.8% (Inagawa and Hirano, 1990). A higher and often quoted prevalence of 5% was shown in another single study (Sekhar and Heros, 1981). A review of retrospective and prospective autopsy and radiographic data by Rinkel and colleagues (1998) showed a rate of 6% in a prospective subgroup of patients studied by angiography. They concluded that "data on prevalence and risk of rupture vary considerably according to study design, study population, and aneurysm characteristics. If all available evidence with inherent overestimation and underestimation is taken together, for adults without risk factors for SAH, aneurysms are found in approximately 2%" (Rinkel et al., 1998). Although most studies have inherent biases, it is generally accepted that the prevalence of unruptured intracranial aneurysms in the population is between 0.8% and 6%.

An important question relates to the incidence of aneurysmal SAH. Many studies exist on this subject and by pooling this data it is generally accepted that the incidence of SAH is between 10 and 15 per 100,000 people per year (Pakarinen, 1967; Sacco et al., 1984; Inagawa et al., 1988; Ingall et al., 1989; Sarti et al., 1991; Truelsen et al., 1998). Based on some of these studies there appears to be an increased incidence in the Finnish and Japanese populations (Pakarinen, 1967; Inagawa et al., 1988; Sarti et al., 1991).

Aneurysmal SAH is an important cause of premature death and occurs most frequently between the ages of 35 and 65 years. The highest incidence is seen in patients between 55 and 60 years of age (Biller et al., 1987). The occurrence of aneurysmal SAH in children or adults older than 80 years of age is rare. Women are affected 1.6 times as frequently as men (Lindsay et al., 1983). Women are also particularly prone to aneurysms of the internal carotid artery (3:2 ratio) while men are more prone to aneurysms of the anterior communicating artery (3:2 ratio).

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Table 39.1

Causes of SAH

Trauma
Spontaneous SAH
1. Saccular aneurysmal rupture—85%
2. Non-aneurysmal perimesencephalic bleeding—10%
3. Arterial dissection, especially vertebral artery dissection—< 5 %
4. Brain arteriovenous malformations
5. Dural arteriovenous fistula—especially tentorial AVF
6. Cervical AVMs and tumors
7. Spinal artery aneurysms
8. Cardiac myxoma
9. Septic aneurysm
10. Pituitary apoplexy
11. Cocaine abuse (often associated with cerebral aneurysms)
12. Anticoagulation
13. Sickle cell disease in children
14. Amyloid angiopathy
15. Vasculitis
16. No identifiable cause

Saccular aneurysms are usually acquired and are believed to result from prolonged hemodynamic stress and subsequent arterial degeneration, particularly at branch points. Hypertension, cigarette smoking, oral contraceptives, alcohol consumption, pregnancy, and cocaine use are all risk factors for aneurysm formation and probably increase the risk of rupture. No causal relationship has been established between physical exertion, emotional stress, and associated aneurysm rupture. Finally the incidence of aneurysms is increased in patients with autosomal dominant polycystic kidney disease, AVMs, moyamoya disease, fibromuscular dysplasia, and other hereditary connective tissue disorders.

39.2.3. Natural history

Recent studies have led to an improvement in the understanding of the natural history of unruptured intracranial aneurysms. In 2003, Wiebers et al. published a prospective multicenter study. The goal of the International Study of Unruptured Intracranial Aneurysms was twofold; to assess the natural history of unruptured aneurysms and to measure the risks associated with their repair. A total of 1,692 patients were followed. Five-year cumulative rupture for aneurysms located on the internal carotid artery, anterior cerebral artery, anterior communicating artery, and middle cerebral artery rates were 0%, 2.6%, 14.5%, and 40% for aneurysms less than 7 mm, 7–12 mm, 13–24 mm, and 25 mm or greater, respectively. Posterior circulation aneurysms, which included posterior communicating artery aneurysms, had rupture rates of 2.5%, 14.5%, 18.4%, and 50%, for aneurysms less than 7 mm, 7–12 mm, 13–24 mm, and 25 mm or greater, respectively (Wiebers et al., 2003). Criticisms of this study regarding the low risk of rupture for small anterior circulation aneurysms include the placement of posterior communicating artery aneurysms in the posterior circulation group, the high number of cavernous sinus aneurysms that usually do not cause SAH, and the unexplained exclusion of a large number of patients. Also, no direct comparison can be made between the surgically and endovascularly treated groups because of significant differences between the two groups and the large number of excluded patients. Despite these criticisms, this remains a very important study in the understanding of the natural history of aneurysmal SAH.

There is a high morbidity and mortality seen in patients with aneurysmal SAH. The overall mortality has been estimated around 50% (range 32–67%) (Broderick et al., 1993; Hop et al., 1997). Hop et al. in a systemic review (1997) showed a recent decline in case fatality rate of 0.5% per year (95% confidence interval, −0.1–1.2).

Results from a cooperative study reveal the peak incidence of rebleeding from a ruptured aneurysm occurs during the first 24 hours (4%) (Nishioka et al., 1984). The cumulative rebleed rate is approximately 19% after the first 2 weeks, 50% during the first 6 months, and 3% per year thereafter. The mortality rate associated with rerupture is reported to be as high as 78% (Nishioka et al., 1984). Only one in three patients with a ruptured aneurysm will return to premorbid state. Associated cognitive deficits are often overlooked and can result in an even higher morbidity with significant effects on the patient's quality of life (Hutter et al., 1999).

Survival and successful treatment from a ruptured aneurysm do not provide cure from the disease because patients with a previous SAH are at risk of developing new aneurysms. There is a 2% annual rate of new aneurysm development in this patient population and up to a five times risk of subsequent aneurysm rupture in new aneurysms (Rinne and Hernesniemi, 1993; van der Schaaf et al., 2005). The 5-year cumulative risk of aneurysmal rupture in previously unruptured aneurysms in patients with prior history of SAH (from another ruptured aneurysm) has been estimated at 1.5–3.5% (Wiebers et al., 2003).

39.2.4. Anatomy

Intracranial aneurysms can be defined by their morphology. The majority are saccular in nature although

fusiform aneurysms occur. Saccular aneurysms are focal protrusions that arise from vessel wall weaknesses at major bifurcations on the arteries along the base of the brain where hemodynamic stress is greatest (Ferguson, 1972). These protrusions are most often spherical in shape but it is not uncommon to have asymmetrical expansion that causes a multilocular appearance. Saccular aneurysms lack the elastic or muscular tissue that is seen in normal arteries. The media and internal elastic lamina end at the aneurysm neck. Saccular aneurysms tend to arise in areas where there is a curve in the parent artery, or in the angle between a major artery and a branch or at branch points (Rhoton, 1980). The anatomic distributions of saccular aneurysms are shown in Fig. 39.1.

An infundibulum is defined as a pyramidal-shaped dilatation at the origins of the arteries less than 3 mm in maximal diameter that usually have a normal media and internal elastic lamina. Infundibula have a much lower risk of rupture than saccular aneurysms and it is important to differentiate between the two. Only a few case reports exist that show progression of infundibula to aneurysms causing SAH (Marshman et al., 1998; Martins et al., 2002; Cowan et al., 2004)

Approximately 85–90% of all saccular aneurysms occur in the anterior circulation and the most common locations are the anterior communicating artery, the internal carotid artery at the origin of the posterior communicating artery, and the middle cerebral artery at the bifurcation. Posterior circulation saccular aneurysms comprise 10–15% of all saccular aneurysms; the most common locations are the basilar apex, vertebrobasilar junction, and the origin of the posterior inferior cerebral artery. It is important to note that aneurysms can occur in either circulation and on any major cerebral vessel (Fig. 39.1).

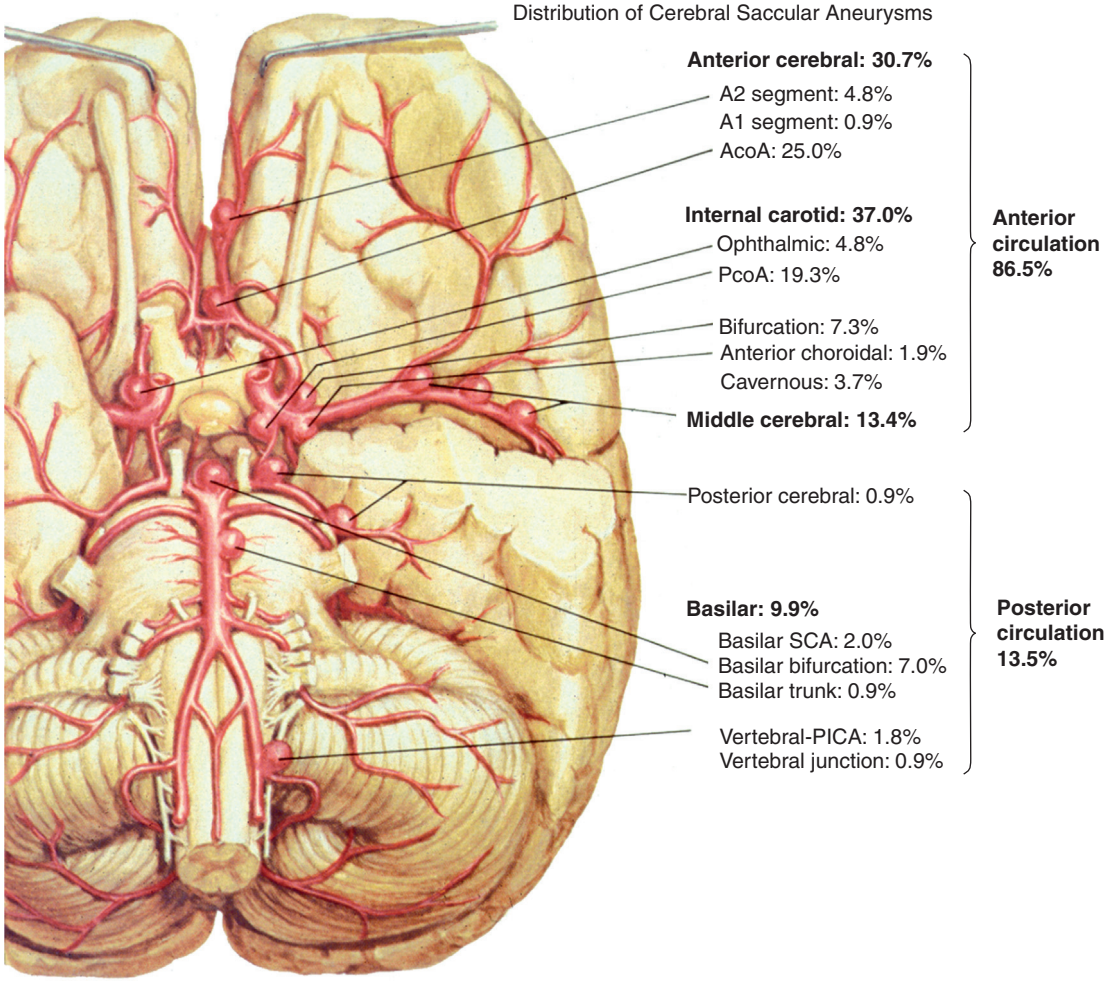

Fig. 39.1. Sites and distribution of cerebral saccular aneurysms. The percentages are based on data reported by Fox and Drake for adults with single aneurysms. PcoA = posterior communicating artery; AcoA = anterior communicating artery; SCA = superior cerebellar artery; PICA = posterior inferior cerebellar artery (from *Netter's Atlas of the Nervous System, Part II: Neurologic and Neuromuscular Disorders*. Modified with permission from ICON (Learning Systems).

Aneurysms are classified as small ($\leq$12 mm), large (13–24 mm) and giant ($\leq$25 mm). Rupture can occur at any size. As previously discussed, Wiebers et al. (2003) showed that smaller size ($<$7 mm) and anterior circulation location may be associated with a lower rate of rupture. However, in practice a significant number of ruptured saccular aneurysms are seen that have sizes smaller than 10 mm. Also in support of this, mathematical models have been created based on blood pressure, wall strength, and total volume of wall substance that predict aneurysmal rupture at 8 mm (Canham and Ferguson, 1985).

It is estimated that approximately 20% of patients with an aneurysm will have multiple aneurysms and this is more common in women (Nehls et al., 1985). In patients with multiple aneurysms, approximately 50% have aneurysms that occur on the opposite side, 20% occur on the same side, and 30% have aneurysms on the midline. This highlights the importance of obtaining four-vessel cerebral angiography after SAH. Difficulty arises in determining which aneurysm has ruptured when multiple intracranial aneurysms are present. Several useful factors to determine which aneurysm ruptured are the area of greatest concentration of blood on computed tomography (CT), the area of vasospasm on angiography, irregularity of aneurysm contour, and largest aneurysm size. When at all possible, multiple aneurysms should be treated by a single surgery or an interventional neuroradiology procedure to minimize the risk of further hemorrhage.

39.2.5. Pathophysiology

Although the exact etiology of saccular aneurysms is unclear, considerable evidence indicates that aneurysms are acquired lesions resulting from complicated interplay of anatomic, hemodynamic, and degenerative factors (Ferguson, 1972). Wall stress at arterial bifurcations caused by pulsatile blood flow is believed to cause local destruction of the internal elastic lamina. Within the aneurysm, turbulent blood flow is thought to contribute to aneurysm growth. With growth of the aneurysm, wall thickness is reduced, and wall tension and rupture risk is increased (Ferguson, 1972; Sekhar and Heros, 1981).

With rupture there is a sudden release of blood into the subarachnoid space. This causes acute meningeal irritation, increased intracranial pressure (ICP), and mass effect on local structures such as the cranial nerves and brain. It is unclear what slows the release of blood after rupture. Several factors such as the size of the aneurysmal tear, the presence of intact cisternal barriers, increased ICP, and local decrease in cerebral blood flow may all contribute to slowing the release of blood. This decreased flow allows for activation of the coagulation cascade and fibrin clot formation.

39.2.6. Genetics of intracranial aneurysm formation

The exact etiology of intracranial aneurysms formation remains unclear. Genetic factors have been implicated. Aneurysms are seen in patients with hereditable connective tissue disorders and familial associated aneurysms. These two topics will be reviewed.

39.2.6.1. Hereditable connective tissue disorders

There are several hereditary connective tissue disorders that have been associated with intracranial aneurysm formation. These include autosomal dominant polycystic kidney disease (ADPKD), Ehlers–Danlos syndrome type IV, α_1-antitrypsin deficiency, Marfan's syndrome, pseudoxanthoma elasticum, and neurofibromatosis type 1. ADPCKD will be reviewed.

39.2.6.2. Autosomal dominant polycystic kidney disease

ADPKD is a systemic disease that affects about 1 in 400–1,000 persons (Fick and Gabow, 1994; Fick et al., 1995). Renal function is generally normal for the first two decades of life but often then deteriorates. Cystic involvement of other organs such as the liver, lungs, and pancreas occurs very frequently (McCarthy and McMullen, 1997).

The reported prevalence of intracranial aneurysms in ADPKD is variable. The overall autopsy incidence is likely 25% and in most of these patients the cause of death was aneurysmal rupture (Schievink et al., 1992). In another study it was estimated that screening will detect aneurysms in 10–25% of ADPKD patients (Huston et al., 1993). A recent study by Rinkel et al. (2005) placed the relative risk at 4.4 times the normal population for developing intracranial aneurysms.

It is important to note that patients with ADPKD seem to be more prone to developing new aneurysms. In one study, on follow-up there is an increased incidence of de novo aneurysms seen at 5-year follow-up (Rinkel, 2005) This was confirmed in a study by Belz et al. (2003) that followed 11 patients with ruptured aneurysms and 9 patients with unruptured aneurysms for 15.2 $\pm$ 8.1 years (range 6.0–33.2 years). New aneurysms were detected in 25% of the patients with either digital subtraction angiography (DSA) ($n = 14$) or magnetic resonance angiography (MRA) ($n = 6$). In contrast to this, a recent study does not suggest an increased risk for growth and rupture, compared to those of intracranial aneurysms in the general population (Gibbs et al., 2004). This data

did not support widespread screening for intracranial aneurysms in the ADPKD population.

Compared with data on patients without ADPKD, SAH in patients with ADPKD occurs not only more often in a familial setting of SAH, but also at an earlier age and more often in men (Gieteling and Rinkel, 2003). In patients with ADPKD, the most frequent site of aneurysms is the middle cerebral artery. The proportion of patients with ADPKD among all patients with SAH is very small (Gieteling and Rinkel, 2003).

Unfortunately, cerebral angiography can lead to a worsening of renal function. MRA is a useful modality to follow these patients with improved safety (Butler et al., 1996; Gibbs et al., 2004). We believe that patients with ADPKD and a positive family history of intracranial aneurysm should undergo screening with MRA because of the natural history of earlier rupture of smaller aneurysms and complications associated with iodinated contrast agents used in computerized tomography angiography (CTA). However, in non-ADPKD patients. CTA is becoming a very useful diagnostic tool in the screening of non-ADPKD patients with intracranial aneurysms.

39.2.6.3. Familial intracranial aneurysms

Some aneurysms may have a genetic link and run in families. In general, these patients are generally younger (average age of 42) and the aneurysms are often smaller at the time of rupture. The genetic inheritance is thought to be autosomal dominant with incomplete penetrance. As previously mentioned, ADPKD, Ehlers–Danlos syndrome type IV and neurofibromatosis type I are hereditary diseases associated with intracranial aneurysms. However, a large majority of familial aneurysms are not associated with any known genetic condition. There has been new interest in familial aneurysms with the commencement of the Familial Intracranial Aneurysm (FIA) study (Broderick et al., 2005).

Several epidemiologic studies have examined the frequency of familial intracranial aneurysms (Norrgard et al., 1987; Schievink et al., 1995; De Braekeleer et al., 1996; Wills et al., 2003). These studies showed that 7–20% of patients that suffered aneurysmal SAH had first- or second-degree relatives with intracranial aneurysms. The FIA study is an ongoing study that is trying to identify the genes related to familial intracranial aneurysm formation. Four-hundred and seventy-five families with affected sib pairs or with multiple affected relatives will be enrolled through retrospective and prospective screening of potential subjects with an intracranial aneurysm (Broderick et al., 2005). The study's long-term goal is to identify genes that underlie the development and rupture of intracranial aneurysms.

Several studies have examined the risk of SAH in patients with familial aneurysms (Bromberg et al., 1995; Schievink et al., 1995; De Braekeleer et al., 1996; Linn et al., 1997). These studies showed an increased risk ratio of SAH from 1.8 to 4.7. It appears there is an increased risk of SAH in first-degree family members of patients with a SAH.

There is also evidence showing that familial aneurysms are larger at the time of diagnosis and are more likely to be multiple (Ruigrok et al., 2004). Also, there is evidence that patients with familial intracranial aneurysms will suffer a SAH at a younger age than patients with spontaneous aneurysms (Bailey, 1993). The combination of increased prevalence, larger size, and earlier rupture are important factors in determining the proper management of these patients. We recommend early investigation and treatment of all family members when two or more siblings or three or more family members are affected.

39.2.7. Clinical presentation of aneurysmal SAH

Major SAH is usually characterized by the acute onset of severe headache that may initially be localized but is more frequently generalized. Over 90% of patients with SAH have headache and it is classically described as the worst headache of the patient's life. Other frequently associated symptoms include nausea, vomiting, and loss of consciousness. Signs of meningeal irritation are often present and include nuchal rigidity (especially seen with flexion) and photophobia. These two signs usually are present within 4–8 hours in most patients. Focal neurological signs and symptoms are often present depending on the size and location of the aneurysm and severity and location of the hemorrhage. Ocular hemorrhages are frequently present on fundoscopy. Subhyoid (preretinal) hemorrhages represent the most frequent hemorrhages and are seen in about 25% of patients (Stiebel-Kalish et al., 2004).

There are several retrospective studies that suggest minor hemorrhages or sentinel hemorrhages may occur in as many as 40% of patients who present with a major rupture (Linn et al., 1994; Polmear, 2003). The symptoms from these sentinel bleeds may clear within a day. It is also speculated that some warning headaches that occur may represent hemorrhage into the wall of the aneurysm without SAH but with local mass effect. It is important to investigate all patients who give a history consistent with a headache that is sudden, severe, and described as the worst of their life.

Aneurysmal compression of the brainstem or cranial nerves may present as focal neurological deficits. Compressive symptoms are commonly caused by intracranial aneurysms. Specific examples are hemiparesis

from pontine compression related to giant aneurysms, non-pupil sparing third-nerve palsy from expanding posterior communicating artery aneurysms, visual loss from ophthalmic artery aneurysms, and facial pain from intracavernous or supraclinoid carotid artery aneurysms. Small infarctions and transient ischemic events due to distal embolization of intra-aneurysmal thrombus may be seen with intracranial aneurysms. Finally, seizures can frequently result secondary to aneurysms or after SAH.

There are two common grading scales used in the clinical assessment of patients with SAH. These scales are shown in Tables 39.2 and 39.3 and also represent important prognostic tools. The prognosis associated with SAH largely depends on the presenting clinical status, which indicates the extent of injury from the initial hemorrhage. The International Cooperative Study showed that mortality sharply increased with decreasing levels of consciousness (Nishioka et al., 1984). Patients with a Hunt Hess grade of 1 or 2 had a 11% mortality, grade 3 had a 27% mortality, grade 4 had a 45% mortality and grade 5 had a 71% mortality (Nishioka et al., 1984).

39.2.8. Diagnostic approach to aneurysmal SAH

When a patient suffers an aneurysmal SAH, the sequence of evaluation begins with a high-resolution, non-contrast CT scan. A good-quality brain CT will detect SAH in more than 97% of patients who undergo the study within 24 hours of hemorrhage (Morgenstern et al., 1998). CT scanning is also very useful to demonstrate the location and extent of hemorrhage which has prognostic significance in predicting the severity of future vasospasm (Fisher et al., 1980). The Fisher scale for CT grading of SAH is shown in Table 39.4. This scale is used to rate the amount of subarachnoid blood. Prognostically, the highest rate of vasospasm is seen in Fisher grade 3 patients and poorest outcome is seen in patients that are Fisher grade 4. A clinical example of a patient with Fisher grade 3 SAH is shown in Fig. 39.2.

In approximately 2.5–5% of patients, SAH is not detected on CT scanning (Morgenstern et al., 1998). It is important that patients with a high clinical suspicion of SAH with a negative CT scan undergo lumbar

Table 39.2

World Federation of Neurological Surgeons Subarachnoid Hemorrhage Grading System (WFNS) (Teasdale et al., 1988)

WFNS grade	Glasgow Coma Score	Motor deficit
0	15	Unruptured aneurysm
1	15	Absent
2	13–14	Absent
3	13–14	Present
4	7–12	Present or absent
5	3–6	Present or absent

Table 39.3

Hunt and Hess Classification of SAH (Hunt and Hess, 1968)

Grade	Description
1	Asymptomatic or mild headache, slight nuchal rigidity
2	Moderate to severe headache, nuchal rigidity, no neurological deficit other than cranial nerve palsy
3	Drowsiness, confusion, or mild focal neurological deficit
4	Stupor, moderate to severe hemiparesis, possible early decerebrate rigidity, and vegetative disturbances
5	Deep coma, decerebrate rigidity, and moribund appearance
Add on grade for serious medical disease (e.g. hypertension, diabetes, severe atherosclerosis, chronic obstructive pulmonary disease or severe vasospasm on angiography)	
Modified classification adds the following criteria (Hunt and Kosnik, 1974)	
0	Unruptured aneurysm
1a	No acute meningeal or brain reaction but patient has a fixed neurological deficit

Table 39.4

Fisher CT scan classification system for subarachnoid hemorrhage (Fisher et al., 1980)

Group	Description
1	No blood detected
2	Diffuse deposition or thin layer of blood, with all vertical layers of blood (interhemispheric fissure, insular cistern, and ambient cistern) < 1 mm thick
3	Localized clots or vertical layers of blood >1 mm in thickness (or both)
4	Diffuse or no subarachnoid blood but with intracerebral or ventricular clots

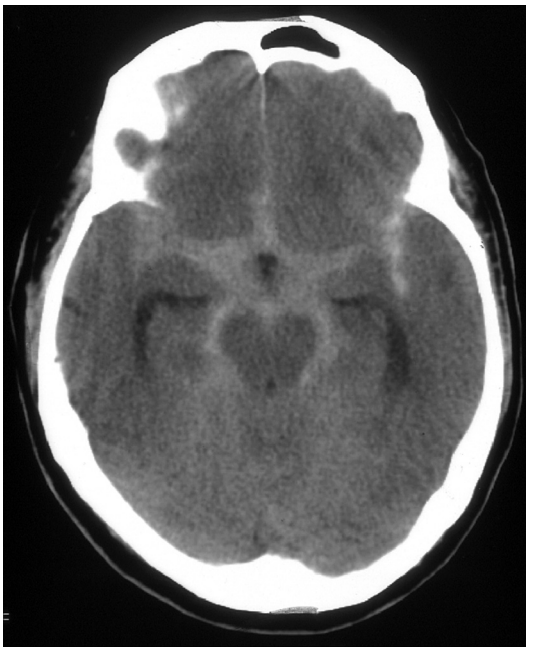

Fig. 39.2. Computed tomography of a Fisher grade 3 SAH from a 15-mm superior cerebellar artery aneurysm. High signal attenuation indicating SAH is centered in the basilar cisterns, with diffuse spread bilaterally into the Sylvian fissures and anteriorly into the interhemispheric fissure.

puncture. This is the most sensitive test for SAH. Typical cerebrospinal fluid findings in SAH are an elevated opening pressure, non-clotting bloody fluid that fails to clear with sequential tubes, xanthochromia (representing hemosiderin) of the supernatant, a red blood cell count of $>100{,}000$ cells/ml, elevated protein, and normal glucose. Since red blood cells in sentinel hemorrhages can be resorbed within 1 or 2 weeks, xanthochromia of the supernatant after centrifugation is diagnostic after SAH and can occur as early as 4–6 hours after hemorrhage and last for weeks.

Cerebral angiography is the "gold standard" for diagnostic evaluation of aneurysms and should be performed in CT-negative or lumbar-puncture-negative SAH patients, or in patients where the clinical suspicion remains high despite negative CT scan and/or inconclusive lumbar puncture. It is very important to obtain four-vessel cerebral angiography that demonstrates both internal carotid arteries and both vertebral arteries. There is a 20% chance of multiple aneurysms in patients with aneurysmal disease. The risk of cerebral angiography is low; most series estimate the mortality to be less than 1% and the rate of permanent neurological morbidity to be less than 0.5% (Willinsky et al., 2003).

Magnetic resonance imaging is not sensitive enough for the detection of acute SAH because acute hemorrhage carries a similar MR signal to the normal brain. Magnetic resonance imaging and specifically magnetic resonance angiography (MRA) are good non-invasive methods for detecting aneurysmal disease (Westerlaan et al., 2004). It is generally accepted that MRA can detect aneurysms ≤ 3 mm but with sensitivities lower than conventional angiography (Okahara et al., 2002). Some studies estimate the false positive rate of MRA to be approximately 16%.

CT angiography (CTA) is a newer tool that is a contrast-based technique. It allows for high-resolution static three-dimensional angiogram images. This is particularly useful in a patient who needs emergency surgery for evacuation of an intracranial hemorrhage or in patients at higher risk of complications from conventional catheter angiography such as ADPKD. CTA is also quite useful as a screening study for asymptomatic aneurysms. At our institution, CTA is a very important tool in the work-up of patients with SAH. Several studies have shown an improved rate of detection and characterization of aneurysm in comparison to DSA (Villablanca et al., 2002a, b). A comparison of the different diagnostic modalities used is shown in Fig. 39.3.

39.2.9. Pathology of SAH

In addition to the hemorrhage into the subarachnoid space, aneurysm rupture can cause hemorrhage within the brain parenchyma, the ventricles, and the subdural space that all worsen the prognosis of SAH. Intracerebral hemorrhage likely occurs when the dome of the aneurysm is embedded within the brain surface. It has also been speculated that recurrent hemorrhages form adhesions which seal off the aneurysms from the subarachnoid space and instead deflect the blood into the brain parenchyma. Intracerebral hematomas are often observed in patients with aneurysmal SAH. The majority of the clots are frontal in location and are usually associated with anterior communicating artery aneurysms. The second most common location is the temporal lobe which is caused by middle cerebral artery aneurysms. Aneurysmal rupture can cause intraventricular hemorrhage. The resultant obstructive hydrocephalus significantly worsens prognosis and requires ventricular cerebrospinal fluid decompression via an external ventricular drain. Anterior communicating artery aneurysms are well known to cause third ventricular hemorrhage by rupturing through the lamina terminalis. Basilar tip aneurysms can cause third ventricular hemorrhage by rupturing through the ventricular floor. Posterior inferior cerebellar aneurysms can rupture through the foramen of Lushka into the fourth ventricle.

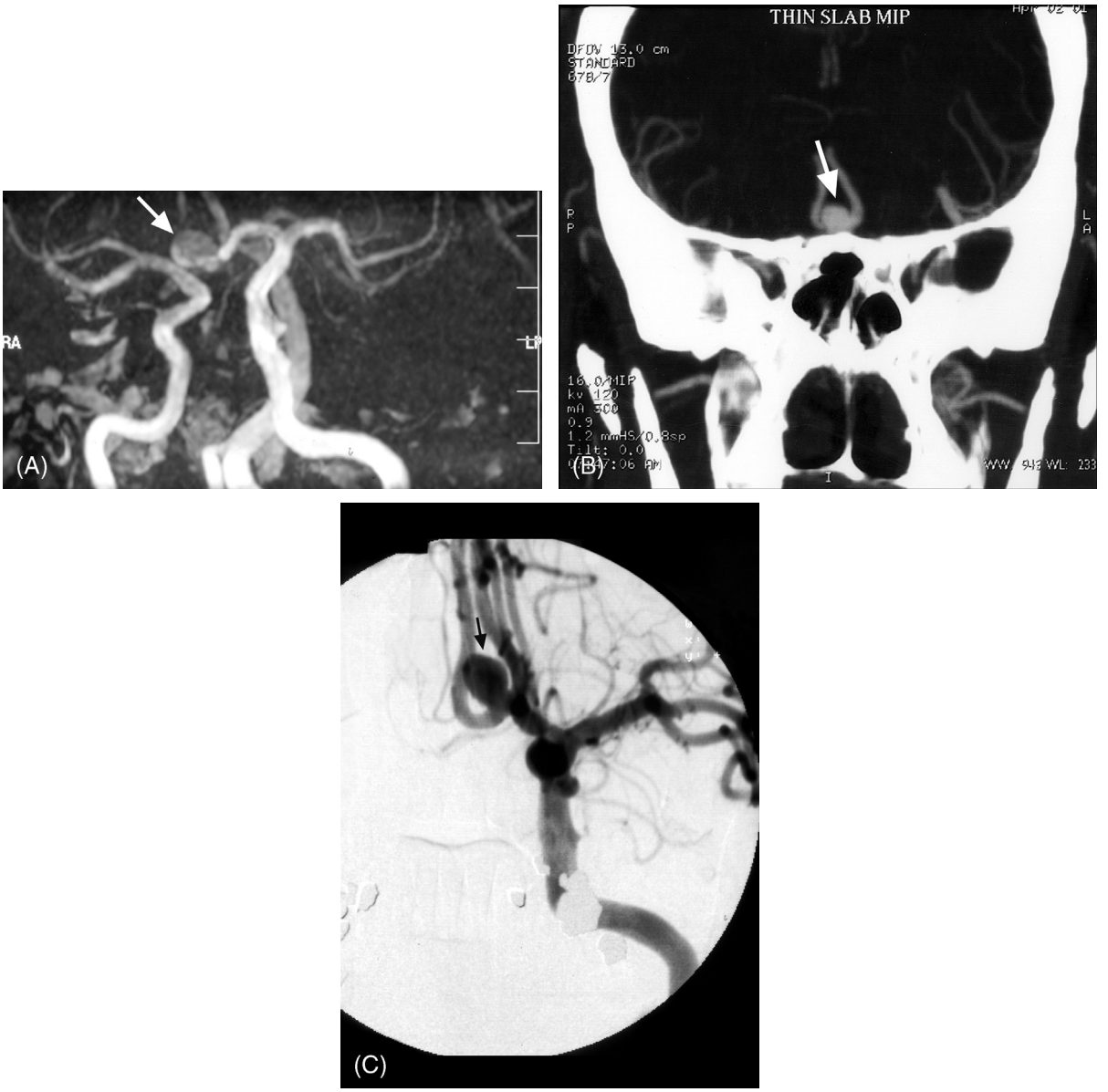

Fig. 39.3. Comparison of imaging modalities. A 7-mm anterior communicating artery aneurysm (arrow) is demonstrated in oblique view on MRA (A) and in AP views on CT angiography (B) and with digital subtraction angiography (C). The aneurysm points superiorly and to the right, and has a base-to-neck ratio of 2:1.

39.2.10. Neurological complications of aneurysmal subarachnoid hemorrhage

The four main complications following rupture of an intracranial aneurysm are cerebral vasospasm, aneurysmal re-hemorrhage, hydrocephalus, and seizures. Cerebral vasospasm is the leading cause of significant morbidity or mortality in patients who survive the initial SAH. It is defined as the sustained narrowing of the cerebral arteries, which occurs after SAH. It rarely presents before the third day and the peak incidence is between days 6 and 8 after SAH. The exact mechanism is not known but one of the leading theories is that lysed erythrocytes release oxyhemoglobin into the subarachnoid space (Asano, 1999; Meguro et al., 2001; Pluta, 2005). The incidence and distribution have been correlated with the thickness and location of the subarachnoid clot. Angiographic vasospasm is seen in 40–70% of patients with SAH. Approximately 20–20% of patients will become symptomatic

and this is defined as clinical vasospasm. It is characterized by insidious onset of confusion and decreased level of consciousness. Focal neurological deficits can occur and are often waxing and waning in nature. Severe vasospasm will cause infarction, ultimately leading to severe neurological morbidity or death. Approximately 20–30% of patients will have clinical vasospasm and of these 10–15% are left with permanent neurological disability or death (Solenski et al., 1995).

The treatment of vasospasm remains problematic. Calcium channel blockers, hypertensive–hypovolemic therapies and endovascular treatment have reduced the overall risk of permanent deficits to 5–10% of all patients with SAH. The influx of intracellular calcium is thought to be one of the major mediators of vascular smooth muscle contraction and vasospasm. The calcium channel nimodipine has been studied in several prospective randomized trials (Allen et al., 1983; Petruk et al., 1988; Pickard et al., 1989, 1990; Barker and Ogilvy, 1996; Feigin et al., 1998; Rinkel et al., 2002, 2005). The largest study is the British Aneurysm Nimpodipine Trial (BRANT) that showed poor outcome and stroke decreased from 33% to 20% without a significant change in vasospasm (Pickard et al., 1989). Nimodipine is given for the first 21 days after aneurysmal SAH or until discharge. It can be speculated that the improved outcomes after nimodipine treatment may be secondary to neuronal protection although this has not been proven.

Blood flow through cerebral vessels can be characterized by Poiseuille's law. Cerebral blood flow is normally controlled by cerebral autoregulation of vessel diameter. In the normal brain, autoregulation maintains a constant vessel diameter and subsequent cerebral blood flow for systolic blood pressures from 50 to 159 mmHg. When this autoregulation is lost, as is seen in cerebral vasospasm, therapies that increase blood flow, decrease blood viscosity and increase perfusion pressure are used. Volume expansion and blood dilution to decrease viscosity is achieved with crystalloids and colloids. Selective peripheral vasopressors are employed to increase cerebral perfusion pressure. This is hypertension–hypervolemia–hemodilution, the so-called "triple-H" therapy (Sen et al., 2003). In cases refractory to "triple-H" therapy, intra-arterial administration of nicardapine or direct angioplasty may be performed.

The goal of early treatment of ruptured aneurysms is to prevent rehemorrhage. Rehemorrhage represents the third most common cause of death in aneurysmal SAH after brain damage caused by the initial hemorrhage and vasospasm. The rate of rebleeding from aneurysms is maximal the first 24 hours after SAH and declines precipitously after the first 48 hours to 1.5% per day for the following 2 weeks (Nishioka et al., 1984). The signs and symptoms of rehemorrhage are the same as the initial hemorrhage with sudden severe headache and possible acute neurological deterioration. Patients that present with a poor clinical grade are at the highest risk of rebleeding. Recurrent SAH is usually more devastating than the initial SAH and the mortality rate associated with the second hemorrhage doubles to approximately 80%. Antifibrinolytic therapies are useful for reducing the rate of rehemorrhage by approximately 40% but do not improve long-term outcome because of increased risk of vasospasm and hydrocephalus (Solenski et al., 1995).

Hydrocephalus is also a common complication after SAH. It is obstructive in nature and is seen in 6–67% of patients depending on the series and the amount of hemorrhage (Dorai et al., 2003; Dehdashti et al., 2004). The clinical manifestations are progressive decreased level of consciousness leading to stupor and possibly deep coma. Hydrocephalus can be confused with vasospasm but can be identified readily with CT scanning. Patients that have intraventricular bleeding from aneurysmal SAH almost universally have hydrocephalus. The treatment of acute hydrocephalus requires placement of an external ventricular drain (EVD), which can cause significant clinical improvement in approximately two-thirds of patients. EVD placement can precipitate a second hemorrhage but this complication can be reduced by careful drainage. Chronic hydrocephalus usually results from blockage of the arachnoid granulations and may need to be treated with ventriculoperitoneal shunting.

In the Cooperative study, seizures were observed in 4.5% of patients with aneurysmal SAH (Nishioka et al., 1984). They are typically seen within the first 2 weeks following hemorrhage and most are seen in the first 24 hours. The pathogenesis is thought to be secondary to local irritation of the brain by blood and early seizures do not predict long-term recurrence in survivors. Patients who experience seizures after SAH should receive appropriate anticonvulsants and if no further seizures occur should be weaned after 6 months to 1 year. No role has been found for the routine administration of anticonvulsants after SAH. Chronic epilepsy after SAH is most commonly seen in patients who have cortical injury by infarction, operative trauma, or gliosis from initial brain injury. These patients will require maintenance anticonvulsant therapy.

39.2.11. Treatment

Ruptured cerebral aneurysms must be treated because without treatment they are most often fatal. Traditionally

they were treated with craniotomy and surgical clipping of the neck of the aneurysm. This is generally considered to be curative if no residual is seen on follow-up angiography. The majority of anterior circulation aneurysms are approached through a frontotemporal (pterional) craniotomy. Depending on location, posterior circulation aneurysms can be approached through frontotemporal, suboccipital, far lateral, and subtemporal approaches. Skull-based techniques combined with hyperventilation, lumbar or ventricular drainage, intravenous diuretic agents and head positioning can be used to minimize brain retraction. Proximal control of arterial feeders is obtained by temporary occlusion of parent vessels either intracranially or extracranially. Temporary occlusion reduces the aneurysm tension and is therefore useful for performing the final neck dissection and preventing intraoperative rupture. However, a recent study showed that duration of occlusion and number of occlusions correlates with ischemic lesions seen on follow-up CT scanning (Juvela et al., 2005).

Electrophysiological monitoring using somatosensory and motor evoked potentials, and brainstem auditory evoked potentials, are useful for detecting early ischemia during temporary occlusion (Sako et al., 1998). Neuroprotective techniques such as pentobarbital-induced electroencephalogram (EEG) isoelectricity, mild hypertension (mean arterial pressure: 100–110 mmHg), and mild hypothermia (temperature: 32–33°C) are often utilized prior to temporary occlusion. Intraoperative mild hypothermia did not improve outcome after craniotomy in good-grade patients after SAH in a multicenter, prospective, randomized trial (Todd et al., 2005). The operating microscope is vital for the dissection of the cerebral arteries, aneurysm neck and aneurysm clip application. To obliterate the aneurysm, titanium clips and appliers of different sizes are applied. There are many studies currently available that show long-term durability with aneurysm clipping.

During the last decade the use of intra-arterial microcatheters has emerged as a viable alternative to craniotomy and aneurysm clipping. With the advent of detachable, thrombogenic platinum coils by Guglielmi et al. (1991) the role of endovascular coil embolization has increased significantly in the treatment of patients with aneurysmal SAH. Affected vessels are catheterized and using fluoroscopy Guglielmi detachable coils (GDC coils) are deposited and repositioned to fit into the aneurysms. Initially, aneurysms with broad necks or a dome-to-neck ratio of < 1 were not amenable to coiling. However, with further developments such as balloon remodeling and intracranial stenting broader based aneurysms can now be effectively treated. Biplane fluoroscopy and three-dimensional angiography have further improved the ability to coil a large variety of aneurysms. Finally there are newer bioactive coils available that may have improved aneurysm obliteration rates and better neck healing and endothelialization (Qureshi, 2004; Katz et al., 2005).

The International Subarachnoid Hemorrhage Trial (ISAT) was published in 2002 (Molyneux et al., 2002). This randomized, multicenter trial was undertaken to compare the safety and efficacy of endovascular coiling to standard neurosurgery clipping for good-grade patients after aneurysmal SAH. Patients ($n = 2{,}143$) were enrolled at centers mainly from the United Kingdom, Europe, and Canada. Patients were selected if it was judged that both coiling and clipping were suitable methods for the ruptured aneurysms treatment. The two study groups were similar in baseline characteristics. Endovascular specialists were required to have previously treated 30 or more aneurysms. The primary outcome was the proportion of patients with a modified Rankin score of 3–6 (dead or disabled) at 1 year. The trial was stopped early by the steering committee because of a statistically better outcome in the coiling patients: 190 of 801 (23.7%) patients allocated to endovascular treatment were dependent or dead at 1 year compared with 243 of 793 (30.6%) allocated to neurosurgical treatment ($p = 0.0019$). The relative and absolute risk reductions in dependency or death after allocation to an endovascular versus neurosurgical treatment were 22.6% (95% CI 8.9–34.2) and 6.9% (95% CI 2.5–11.3), respectively. The risk of rebleeding from the ruptured aneurysm after 1 year was two per 1,276 and zero per 1,081 patient-years for patients allocated endovascular and neurosurgical treatment, respectively (Molyneux et al., 2002). The authors concluded that "in patients with a ruptured intracranial aneurysm, for which endovascular coiling and neurosurgical clipping are therapeutic options, the outcome in terms of survival free of disability at 1 year is significantly better with endovascular coiling. The data available to date suggest that the long-term risks of further bleeding from the treated aneurysm are low with either therapy, although somewhat more frequent with endovascular coiling." They also concluded that "the risk of bleeding from aneurysm coiling appears to be low" (Molyneux et al., 2002).

There are several criticisms of the ISAT study (Diringer, 2005). A large percentage of patients were excluded because either surgery or coiling were the preferred techniques. The majority of the study patients were from the UK. There was no requirement for the surgeons to have treated a preset number of patients prior to being in the study. The duration of follow-up and use of a mail questionnaire has also been criticized. Finally, the greatest criticism is that there is relatively short

angiographic follow-up and the durability of coiling for aneurysmal SAH is not currently known (Diringer, 2005). Regardless of the criticisms, this is a landmark study that has resulted in an increase in the use of coil embolization for all types of patients with intracranial aneurysms.

Surgical repair is often recommended in young, healthy patients that otherwise would have to undergo multiple follow-up catheter angiograms if they had coiling. Also, patients that require evacuation of intracerebral hematomas are best treated with surgical clipping. Other aneurysms where clipping is selected over coiling are complex anterior communicating and middle cerebral artery aneurysms that have broad necks and perforating or distal branches arising from the aneurysm. If coiled, there is a high risk of infarction in this subgroup of patients. Clipping is also useful in the treatment of large aneurysms causing mass effect because the aneurysm can be resected and mass effect relieved. Figures 39.4 and 39.5 illustrate surgical clipping of aneurysms.

Coiling is very useful for posterior circulation aneurysms that can be difficult to access with surgical approaches. Poorer grade aneurysm patients and patients medically unfit for craniotomy are also best treated with coiling. Figure 39.6 illustrates the use of coil embolization in the treatment of large left superior cerebellar artery aneurysm. We feel that aneurysms should be treated at tertiary referral centers that provide both endovascular and cerebrovascular surgery treatments. A multidisciplinary group is best able to decide on the best treatment in unbiased manner.

39.3. Other causes of SAH

Aneurysmal SAH represents 80–85% of all causes of SAH (Rinkel et al., 1993). Perimesencephalic hemorrhage represents 10% and the remaining 5% are caused by various other conditions (Adams and Gordon, 1991; Rinkel et al., 1993) (Table 39.1).

39.3.1. Non-aneurysmal perimesencephalic hemorrhage

Perimesencephalic hemorrhage represents approximately 10% of all causes of SAH (Adams and Gordon, 1991; Rinkel et al., 1993). Another name for this condition is pretruncal hemorrhage (Schievink and Wijdicks, 1997). Most patients that present with this condition are adults and often in their sixth decade (Van Gijn and Rinkel, 2001). The clinical symptoms are similar and often indistinguishable from aneurysmal SAH. Some authors have shown that in certain patients the headaches can be more gradual in onset and reach a maximum intensity in minutes as opposed to seconds as is seen in aneurysmal SAH (Canhao et al., 1995; Linn et al., 1998; Van Gijn and Rinkel, 2001). One of the most important clinical findings in aiding with eventual diagnosis is the excellent clinical status of the patients (Van Gijn et al., 1985; Van Gijn and

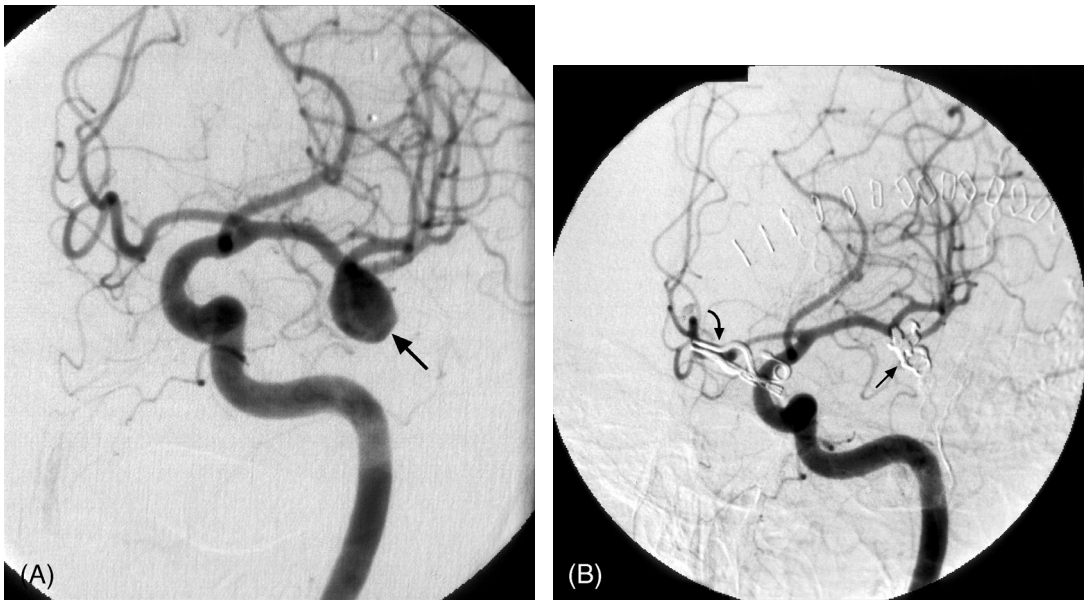

Fig. 39.4. Clip occlusion of a large left middle cerebral artery (MCA) aneurysm. (A) Digital subtraction angiography of a 15-mm left MCA bifurcation aneurysm (arrow) seen in the AP view. (B) Post-operative angiogram also seen in AP view shows occlusion of the MCA aneurysm by clip (straight arrow). A 6-mm anterior communicating artery aneurysm was also concomitantly treated with clip occlusion (curved arrow).

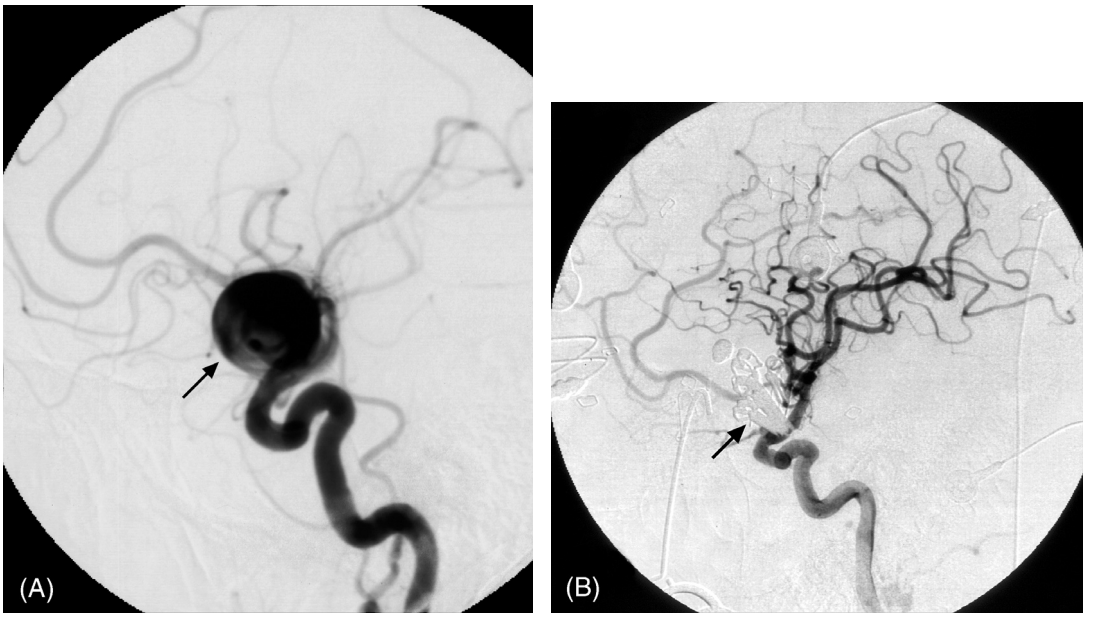

Fig. 39.5. Giant left paraclinoid internal carotid artery (ICA) aneurysm. (A) Digital subtraction angiography demonstrates a 2.5-cm aneurysm (arrow) originating from the left paraclinoid ICA. (B) Post-operative angiogram shows occlusion of the aneurysm using multiple clips (arrow).

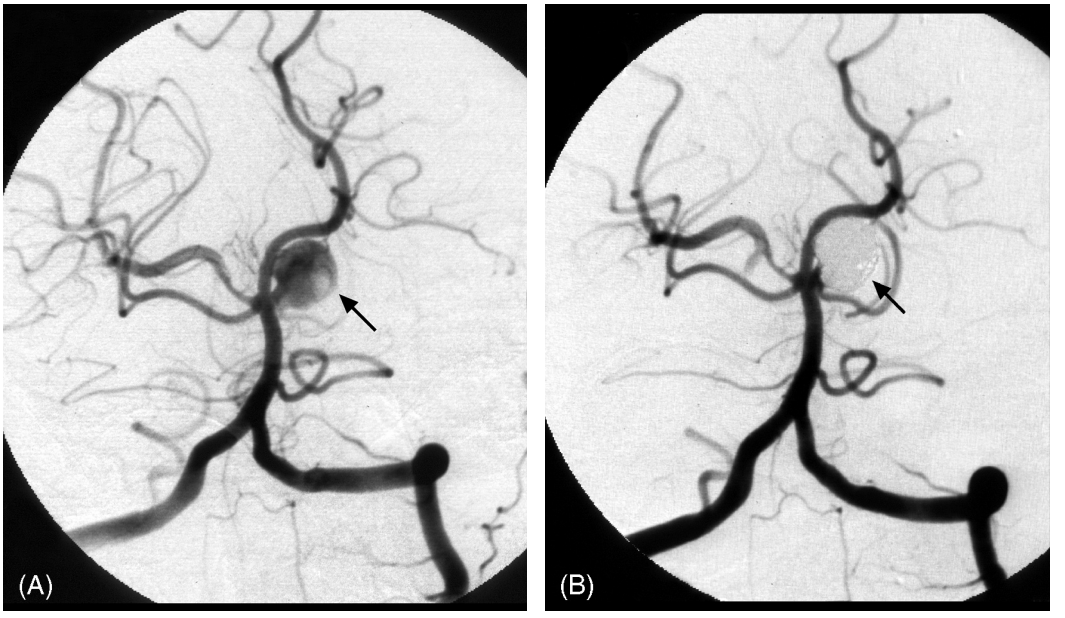

Fig. 39.6. Coil embolization of a large left superior cerebellar artery (SCA) aneurysm. A digital subtraction angiogram demonstrating the 15-mm left SCA aneurysm that ruptured, resulting in the hemorrhage shown in Fig. 39.2. AP views show aneurysm (arrow) prior to treatment (A) and near complete obliteration of aneurysm following placement of GDC coils (B, arrow).

Rinkel, 2001). It is extremely unusual to see long-term neurological sequelae associated with this condition.

The exact etiology of the condition is unknown but several authors have speculated as to a venous origin (Watanabe et al., 2002; Van der Schaaf et al., 2004). A recent study analyzed the CTA results of 55 patients with perimesencephalic hemorrhage and 42 patients with aneurysmal SAH. They found primitive venous drainage into the dural sinuses instead of the normal pattern into the vein of Galen in 53% of patients with perimesencephalic bleed compared to 19% of patients with aneurysmal SAH (Van der Schaaf et al., 2004).

The pattern of bleeding on CT imaging is important in establishing the diagnosis. In the majority of patients the blood is perimesencephalic in location and therefore directly anterior to midbrain and pons (Van Gijn et al., 1985; Rinkel et al., 1991; Zentner et al., 1996; Van Gijn and Rinkel, 2001). In 20% of patients, dilatation of the lateral ventricles is seen but few of these patients require a permanent cerebrospinal fluid diversion procedure (Rinkel et al., 1992). SAH can also be seen in the quadrigeminal, ambient, and crural cisterns in some patients (Van Gijn et al., 1985; Van Gijn and Rinkel, 2001).

The radiological diagnosis of non-aneurysmal perimesencephalic hemorrhage is one of exclusion. This is important because 2.5–5% of patients with perimesencephalic hemorrhage may have ruptured posterior circulation aneurysms (Pinto et al., 1993; Van Calenbergh et al., 1993; Van Gijn and Rinkel, 2001). It is important to identify a strategy for the investigation of patients with suspected perimesencephalic hemorrhage. According to Van Gijn and Rinkel (2001), the 5% chance of finding an aneurysm in patients with a typical pattern of perimesencephalic blood must be weighed against the risks of catheter angiography. Another study reports a high rate of rebleeding in patients with an aneurysmal pattern of bleeding but three negative cerebral angiograms (Ruigrok et al., 2002). Velthuis et al. (1999) showed that good recognition of perimesencephalic hemorrhage is possible on unenhanced CT and that CTA accurately excludes and detects vertebrobasilar aneurysms. They conclude that DSA can be withheld in patients with a perimesencephalic pattern of hemorrhage and negative CTA (Velthuis et al., 1999). It is important to have an experienced neuroradiologist available for interpretation of the images. At our institution, patients with classic perimesencephalic bleeding pattern on non-contrast-enhanced CT are investigated with DSA followed by either CTA or DSA at 3–6 weeks.

The prognosis in patients with perimesencephalic hemorrhage is excellent (Ildan et al., 2002; Ruigrok et al., 2002). Their clinical course is uneventful and the majority of patients return to normal daily activities and work (Rinkel et al., 1990; Brilstra et al., 1997; Van Gijn and Rinkel, 2001). Rebleeding is extremely rare.

39.3.2. Vertebral arterial dissection

Vertebral artery dissection can cause SAH and has a high propensity to rebleed. Dissection of the carotid artery occurs more frequently but rarely causes SAH. The precise incidence of SAH from vertebral artery dissection is not known but it is likely to be less than 5% (Sasaki et al., 1991; van Gijn and Rinkel, 2001).

Vertebral artery dissections can be classified as spontaneous or post-traumatic. Spontaneous dissections have been associated with genetic and environmental factors. Genetic factors include fibromuscluar dysplasia, Ehlers–Danlos syndrome type IV, Marfan's syndrome, and ADPKD (Kalb, 2001; Schievink, 2001; Schievink et al., 2002). Environmental factors often relate to a minor traumatic events that involve sudden neck movements (Schievink, 2001). In some patients the dissection is secondary to severe head and spinal trauma (Guyot et al., 2001). Spinal manipulative therapy has also been implicated as a cause of vertebral artery dissection (Smith et al., 2003). Finally, dissecting aneurysms of the vertebral artery can result from vertebral artery dissection (Shimoji et al., 1984; Caplan et al., 1988). These aneurysms tend to be fusiform in nature.

Neurological deficits in patients with vertebral artery dissection and SAH can include palsies of cranial nerves IX and X, Wallenberg's syndrome, and other syndromes of brainstem and cerebellar ischemia (Senter and Sarwar, 1982; Caplan et al., 1988; Savitz and Caplan, 2005). The most important aspect of vertebral artery dissection with associated SAH is the high rate of rebleeding. This rate has been estimated at between 30% and 70% (Caplan et al., 1988; van Gijn and Rinkel, 2001; Yamada et al., 2004). It is therefore recommended that all patients with vertebral artery dissection with or without a dissecting aneurysm be treated (Ramgren et al., 2005). Treatment options include craniotomy and clipping of the aneurysm or trapping of the vertebral artery, and endovascular stenting or vertebral artery occlusion (Hamada et al., 2003; Kai et al., 2004; Chiche et al., 2005; Sheah et al., 2005). Endovascular techniques are advantageous because they are minimally invasive, allow preocclusion balloon testing and do not preclude open surgical techniques if they fail (Sheah et al., 2005). Patients with SAH should not be anticoagulated.

39.3.3. Traumatic subarachnoid hemorrhage

Traumatic SAH frequently occurs after closed head injuries. Overall it is the most common cause of SAH. Recent studies have shown its presence to be a powerful factor for a poor outcome. A study evaluated 141 consecutively admitted patients with traumatic SAH (Chieregato et al., 2005). This study showed the outcome of patients with traumatic SAH at admission was related in a logistic regression analysis to the admission Glasgow Coma Scale score and to the amount of subarachnoid blood (Chieregato et al., 2005). The amount of subarachnoid blood and the presence of associated parenchymal damage are powerful independent factors associated with a worsening appearance on CT, thus linking poor outcomes and CT changes (Chieregato

et al., 2005). Other studies also provide evidence that traumatic SAH is associated with worse outcome (Soustiel et al., 1998, 2002; Mattioli et al., 2003; Fainardi et al., 2004; Soustiel and Shik, 2004).

The utility of calcium channel blockers in patients with aneurysmal SAH has been proven in several trials (Allen et al., 1983; Petruk et al., 1988; Pickard et al., 1989, 1990; Barker and Ogilvy, 1996; Feigin et al., 1998; Rinkel et al., 2002, 2005). A recent systemic review showed a beneficial effect of nimodipine in a subgroup of patients with traumatic SAH although there were a significant number of adverse reactions in the intervention group (Langham et al., 2000, 2003). Further research and clinical trials are needed to study novel treatment options with traumatic SAH to improve patient outcome. The presence of SAH is an important prognostic finding in trauma patients.

39.3.4. Other causes of SAH

Cerebral AVMs rarely rupture into the subarachnoid space to cause SAH. Its estimated occurrence is less than 5% of all AVMs that bleed (van Gijn and Rinkel, 2001). It is more likely that associated prenidal or intranidal aneurysms caused the SAH than the AVM itself (Thompson et al., 1998; Fleetwood and Steinberg, 2002). Dural arteriovenous fistula can be associated with SAH. Dural arteriovenous fistulas that have retrograde leptomeningeal cortical drainage without drainage by a major sinus have the highest risk of bleeding. Cervical spinal AVMs can cause intracranial SAH (van Gijn and Rinkel, 2001). Cervical spinal tumors and specifically hemangioblastoma, which can be associated with Von Hippel Lindau syndrome, can also cause SAH (Kormos et al., 1980; Cervoni et al., 1995; Irie et al., 1998; Minami et al., 1998; Berlis et al., 2003).

39.4. Conclusions

SAH can result from many etiologies. The most frequent overall cause is trauma but aneurysmal SAH accounts for 85% of all non-traumatic causes. Rapid medical stabilization followed by appropriate investigations and management are important in improving patient outcomes. Diagnostic imaging has improved significantly over the last 15 years but further work is needed. A better understanding and treatment of vasospasm will lead to improved patient outcomes. Finally, patients with SAH are best managed at multidisciplinary centers with appropriate interventional neuroradiology, neurosurgery, neurology, and critical care support.

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Chapter 40

Cerebral venous thrombosis

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Thrombosis of the dural sinus and encephalic veins (cerebral venous thrombosis, or CVT) was until recently considered a rare, often fatal disease (Krayenbühl, 1967; Lefkowitz, 1989), related to the puerperium (Cantu and Barinagarrementeria, 1993) and to infection of the central nervous system, sinuses, and mastoid (Einhäupl et al., 1990; Bousser and Russell, 1997). The introduction of magnetic resonance imaging (MRI) in clinical practice dramatically modified this picture. CVT became recognized with increasing frequency and its clinical spectrum has widened considerably. CVT is a disease of interest not only for neurologists and neurosurgeons but also for internists, oncologists, hematologists, and obstetricians.

40.1. Epidemiology and demography

CVT is less frequent than other types of stroke. In large teaching hospitals, about 5–10 patients with CVT are admitted yearly. A community study performed in England and Wales found an incidence of 22 cases per annum (Kalbag and Woolf, 1967). The prevalence of CVT in autopsies is high: 9% (Towbin, 1973). Autopsy studies are naturally biased to severe fatal cases, in particular to those associated with intracranial infection, which are fortunately rare nowadays. This high number could not be reproduced in a recent study (Bienfait et al., 2003), which found only 1% in consecutive autopsies. In a nationwide hospital-based series in Portugal, including all neurology services, 91 new cases of CVT were identified, corresponding to an incidence of 0.22/100,000/year (95% confidence interval, 0–47) (Ferro et al., 2001). A hospital discharge registry in the USA gave an incidence of CVT during pregnancy of 11.6/100,000 deliveries (Lanska and Kryscio, 2000). The incidence in the multicenter Canadian registry of CVT in infants and children aged less than 18 years was 0.64/100,000 (DeVeber et al., 2001). The incidence of CVT is probably underestimated because of the difficulty of case ascertainment: CVT has a rather variable clinical presentation and there is a need to perform MRI/angiography to confirm the diagnosis.

CVT is more common in neonates than in older children (DeVeber et al., 2001). In adults CVT affects patients younger than those with other types of strokes. In the large International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT) cohort the mean age was 39 years (Ferro et al., 2004). Nevertheless 8% of the patients were older than 65 (Ferro et al., 2005a). CVT is more common in females than in males (female/male ratio 2.9:1) (Ferro et al., 2004).

40.2. Anatomy

Blood of the brain is drained by cerebral veins, which are arranged into a superficial and deep venous system. Superficial veins are quite variable in number and location, and drain blood from the major part of the cerebral cortex, with the exception of the inner face of the temporal and occipital lobes. The deep cerebral veins (basal veins of Rosenthal, internal cerebral veins, and the great cerebral vein of Galen) drain blood from the basal ganglia, diencephalon, and deep white matter of cerebral hemispheres. Apart from the anatomical variations of the basal veins, the deep venous system is relatively constant compared to the superficial cortical venous system. Posterior fossa veins are quite variable in their number and course.

Cerebral veins drain the blood into the dural sinus, which are endothelial-lined channels without valves, enclosed between fibrous layers of the dura mater.

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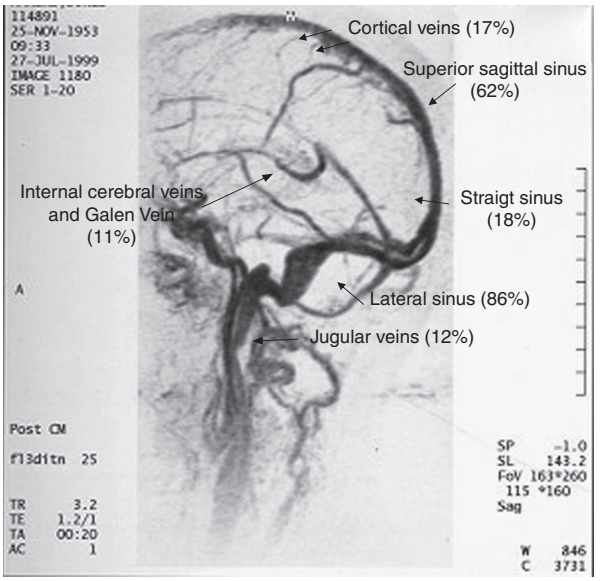

Fig. 40.1. Anatomy of the cerebral venous system. The relative frequency of involvement are given in parenthesis (data from the International Study of Cerebral Vein and Dural Sinus Thrombosis) (Ferro et al., 2004). In most patients thrombosis occurs in more than one sinus.

Superficial veins drain into the superior sagittal sinus (SSS) and lateral sinuses, and the deep cerebral veins into the straight sinus and lateral sinuses (Fig. 40.1). Cavernous sinuses drain most of the blood from the face and the anterior part of the brain, and connect with the lateral sinuses via superior and inferior petrosal sinuses and with the pterygoid plexus. There are several anastomoses between the dural sinuses and extracranial veins.

Most of the cerebral venous blood flows posteriorly, from the superior sagittal sinus or the straight sinus via the lateral sinuses into the internal jugular veins. A smaller proportion flows to the cavernous sinuses. There are numerous anatomical variations in the dural sinuses. The most important are: hypoplasia of the anterior part of the SSS; duplication of the SSS, mainly in its posterior part; asymmetry of the lateral sinus, aplasia, or hypoplasia of its proximal part, more often on the left. The straight sinus may join the torcular, the right transverse sinus, the left transverse sinus, or both.

40.3. Pathophysiology

The pathophysiology of CVT remains largely unknown, partly because of the high variability of the venous system anatomy and the lack of experiments in adequate animal models of CVT (Schaller and Graf, 2004). Recently, advances in imaging modalities such as diffusion- and perfusion-weighted magnetic resonance have contributed to our understanding of the pathophysiological differences between venous and arterial occlusion (Corvol et al., 1998; Lövblad et al., 2001; Yoshikawa et al., 2002).

Obstruction of the venous structures causes increased venous pressure, reduced capillary perfusion pressure and increased cerebral blood volume. Dilatation of cerebral veins and recruitment of collateral pathways may initially compensate for changes in pressure. Blood flow in veins with poor collateral flow will become slow and might contribute to extension of the thrombosis.

The increase in venous and capillary pressure leads to blood–brain barrier disruption, causing vasogenic edema, with leakage of blood plasma into the interstitial space. As intravenous pressure increases, progression from mild parenchymal change to severe cerebral edema and venous hemorrhage may occur due to venous or capillary rupture. The increase of intravenous pressure produces intracerebral venous congestion, increases intravascular pressure and lowers cerebral perfusion pressure. The decrease of cerebral blood flow (CBF) is associated with a failure of energetic metabolism leading to intracellular entry of water due to failure of the Na^+–K^+–ATPase pump, and consequent cytotoxic edema (Gotoh et al., 1993). MRI has demonstrated the co-existence of both types of edema, cytotoxic and vasogenic (Rother et al., 1996; Corvol et al., 1998; Chu et al., 2001; Yoshikawa et al., 2002) in patients with CVT.

After venous occlusion, large areas of the brain may be functionally and metabolically disturbed, but not irreversibly. If collateral pathways drain the blood, adequate blood perfusion may be possible, and swollen brain cells may be functionally impaired but potentially recoverable (Frerichs et al., 1994).

Another effect of venous thrombosis, besides parenchymal changes, is impairment of CSF absorption which causes intracranial hypertension. CSF absorption occurs in the arachnoid granulations and CSF is drained into the SSS. Thrombosis of the sinuses leads to increased venous pressure, impaired CSF absorption, and consequently increased intracranial pressure. It is more frequent if the SSS is occluded, but it may also result from a rise in sinus pressure without thrombosis of the SSS, such as in jugular vein thrombosis.

40.5. Clinical aspects

In contrast with other types of stroke, CVT has a highly variable clinical presentation (Bousser et al., 1985; Bousser and Russell, 1997). Besides an acute presentation, CVT can have a more protracted subacute or chronic course. A TIA-like presentation has also been reported (Ferro et al., 2000). Clinical

symptoms and signs depend on the site and number of occluded sinus and veins, on the presence of parenchymal lesions, on the age of the patient (DeVeber et al., 2001; Ferro et al., 2005a) and on the interval from onset to presentation (Ferro et al., 2005b). Symptoms and signs can be grouped in three syndromes that are useful for the front-line physician: isolated intracranial hypertension (headache with or without vomiting, papilledema and visual symptoms) (Biousse et al., 1999), focal syndrome (focal deficits, seizures, or both) and encephalopathy (multifocal signs, mental status changes, stupor/coma) (Bousser and Russell, 1997; Ferro et al., 2001). Figure 40.2 shows the frequency of symptoms and signs in the ISCVT cohort.

Headache is the most frequent symptom. As with other secondary headaches, headaches associated with CVT are more frequent in women and young patients. They are usually the first (and sometimes the only) symptom of CVT, or precede by days or weeks other symptoms or focal signs. The site of the headaches has no localizing value; that is, it has no relationship with the localization of the occluded sinus or of the parenchymal lesions (Ameri and Bousser, 1993; Lopes et al., 2000).

The type of headache associated with CVT has not yet been described prospectively. CVT-associated headaches are more severe and of more acute onset than other types of headaches requiring emergency care (Iurlaro et al., 2003), with the exception of subarachnoid hemorrhage. The most frequent type of headache is the intracranial hypertension type, a severe, dull, generalized head pain worsening with Valsalva maneuvers and with recumbence. Visual obscuration may occur coinciding with bouts of increased intensity of the headache. Other types of headache have been also described in CVT, such as migraine with aura (Newman et al., 1989; Martins et al., 2001; Slooter et al., 2002) and thunderclap headache (de Bruijn et al., 1996). A few cases of CVT mimicking subarachnoid hemorrhage have been reported, presenting with sudden headache and neck stiffness only (Sztajzel et al., 2001). Because lumbar puncture can precipitate a CVT, CVT must also be included as a possible cause of persisting headache following lumbar puncture (Canhão et al., 2005a).

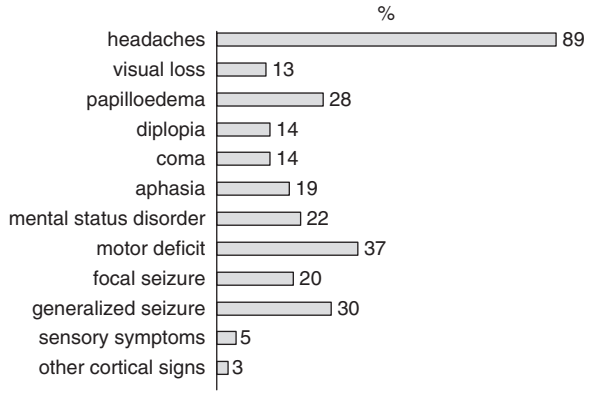

Fig. 40.2. Clinical presentation of patients with cerebral vein and dural sinus thrombosis (Ferro et al., 2004).

Patients with a chronic course or delayed clinical presentation may show papilledema on funduscopy, a finding less frequent in acute cases (Ferro et al., 2005b). In severe acute cases disturbances of consciousness and mental troubles, such as delirium, apathy, or a frontal lobe syndrome are often present. Motor deficits, mono- or hemiparesis, sometimes bilateral, are the most frequent focal deficits. Aphasia, in particular of the fluent type, may follow sinus thrombosis, especially of the left lateral sinus. Sensory deficits and visual field defects are less common. Focal or generalized seizures, including status epilepticus are more frequent than in other stroke types. Seizures are more frequent in patients with motor or sensory defects and in those with parenchymal lesions (Ferro et al., 2003). Multiple cranial nerve palsies (Collet–Sicard syndrome) may occur in rare instances of lateral sinus (Kuehnen et al., 1998), jugular or posterior fossa vein thrombosis. A pulsatile tinnitus may be the sole symptom of a jugular vein or lateral sinus thrombosis (Utz et al., 1997; Waldvogel et al., 1998).

The clinical presentation of CVT varies accordingly to the presence of parenchymal lesions and with the location of the occluded sinus or vein. Not surprisingly, if a patient has a parenchymal lesion he is more likely to be comatose or to have motor deficits or aphasia and seizures, and less likely to present with isolated headache. Nowadays rare cavernous sinus thrombosis, ocular signs dominate the clinical picture with orbital pain, chemosis, proptosis, and oculomotor palsies. The uncommon and difficult to diagnose isolated cortical vein occlusion produces motor/sensory deficits and seizures (Jacobs et al., 1996; Ahn and Roh, 2003; Cakmak et al., 2004; Duncan et al., 2005). In occlusion of the sagittal sinus, motor deficits, bilateral deficits, and seizures are frequent while presentation as an isolated intracranial hypertension syndrome is infrequent. The opposite is found in patients with isolated thrombosis of the lateral sinus, who often present with isolated intracranial hypertension. If the left transverse sinus is occluded, aphasia often follows. When the deep cerebral venous system is occluded the clinical picture may be more severe with coma, mental symptoms and motor deficits, often bilateral (Crawford et al., 1995; Lafitte et al., 1999; Lacour et al., 2000). More limited thrombosis of the deep venous system

can produce relatively mild symptoms (van den Bergh et al., 2005).

Age also modulates the clinical picture. In children diffuse signs of brain damage with coma and seizures are the main manifestations, especially in neonates. Clinical manifestations in older children may resemble the adult ones, with headache and hemiparesis (Lancon et al., 1999; De Veber et al., 2001). Elderly patients also have a distinctive clinical picture: decreased vigilance and mental symptoms are more common, while headaches and isolated intracranial hypertension are less frequent than in younger patients (Ferro et al., 2005a).

40.6. Diagnosis

The confirmation of the diagnosis of CVT is based on neuroimaging. In clinical practice, computed tomography (CT) is usually the first investigation to be performed. It is useful to rule out other acute cerebral disorders, but may be normal in up to 30% of cases, and most of the findings are non-specific. CT may show direct or indirect signs of CVT (Bousser and Russell, 1997) (Fig. 40.3). Direct signs can be found in about one-third of cases, such as empty delta sign visible after contrast injection, the cord sign and the dense triangle sign. Indirect signs are more frequent and include: intense contrast enhancement of falx and tentorium, dilated transcerebral veins, small ventricles, and parenchymal abnormalities. Parenchymal abnormalities may occur in 60–80% of cases and comprise: white matter hypodensity due to diffuse brain edema, one or more hyperdensities suggestive of hematoma or hemorrhagic infarcts, areas of hypodensity reflecting edema or infarction, and areas of gyral enhancement. In serial CT these lesions may disappear ("vanishing infarcts") or new lesions may appear. CT venography is a promising technique to visualize the cerebral venous system and to diagnose CVT, demonstrating filling defects, sinus wall enhancement, and increased collateral venous drainage (Casey et al., 1996; Majoie et al., 2004). When combined with CT it adds considerable information in suspected CVT cases (Wetzel et al., 1999).

Magnetic resonance imaging (MRI) combined with magnetic resonance angiography (MRA) is the most sensitive examination technique for the diagnosis of CVT (Dormont et al., 1994; Lafitte et al., 1997) (Fig. 40.4). Direct visualization of the thrombus confirms the diagnosis of CVT. The characteristics of the signal depend on the age of the thrombus: in the first five days they are isointense on T1-weighted images and hypointense on T2-weighted images. After this time the diagnosis becomes easier due to an increased signal on both T1- and T2-weighted images, and after the first month there is a variable pattern of signal, which may become isointense (Dormont et al., 1994; Isensee et al., 1994). The combination of an abnormal signal in a sinus and a corresponding absence of flow on MRA supports the diagnosis of CVT. Nevertheless, there are some diagnostic pitfalls with these techniques (Ayanzen et al., 2000) and the diagnosis of cortical vein thrombosis remains difficult to establish. Gradient-echo T_2*-weighted images improve the diagnosis of CVT

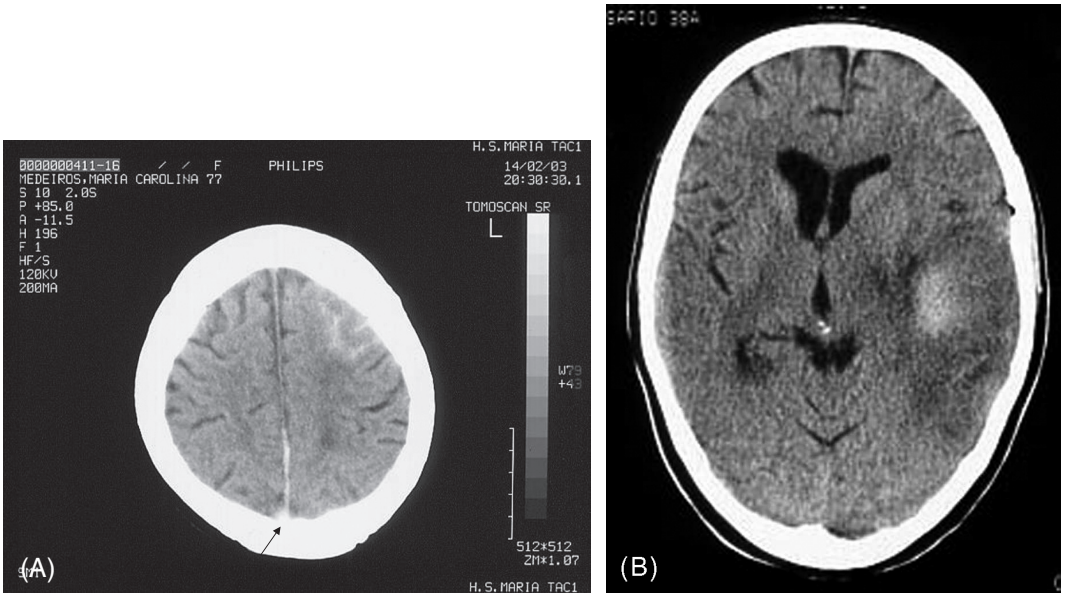

Fig. 40.3. CT imaging of sinus thrombosis. (A) Subarachnoid hemorrhagic densities and the dense triangle sign (arrow) in a patient with thrombosis of the superior sagittal sinus. (B) Left hemorrhagic infarct in lateral sinus thrombosis.

enabling the identification of isolated cortical venous thrombosis as a hypointense area (Cakmak et al., 2004; Selim et al., 2002; Fellner et al., 2005).

MRI is also useful in showing the parenchymal lesions secondary to venous occlusion: brain swelling, edema, or infarction demonstrated as hypo- or isointense lesions on T1-weighted images and hyperintense on T2-weighted images, or hemorrhagic infarcts, appearing as hyperintense lesions in both MRI sequences.

At present, intra-arterial angiography is performed mainly when the diagnosis of CVT is doubtful, namely in the rare cases of isolated cortical vein thrombosis. Typical signs of CVT are the non-visualization of all or part of a sinus, delayed emptying with collaterals

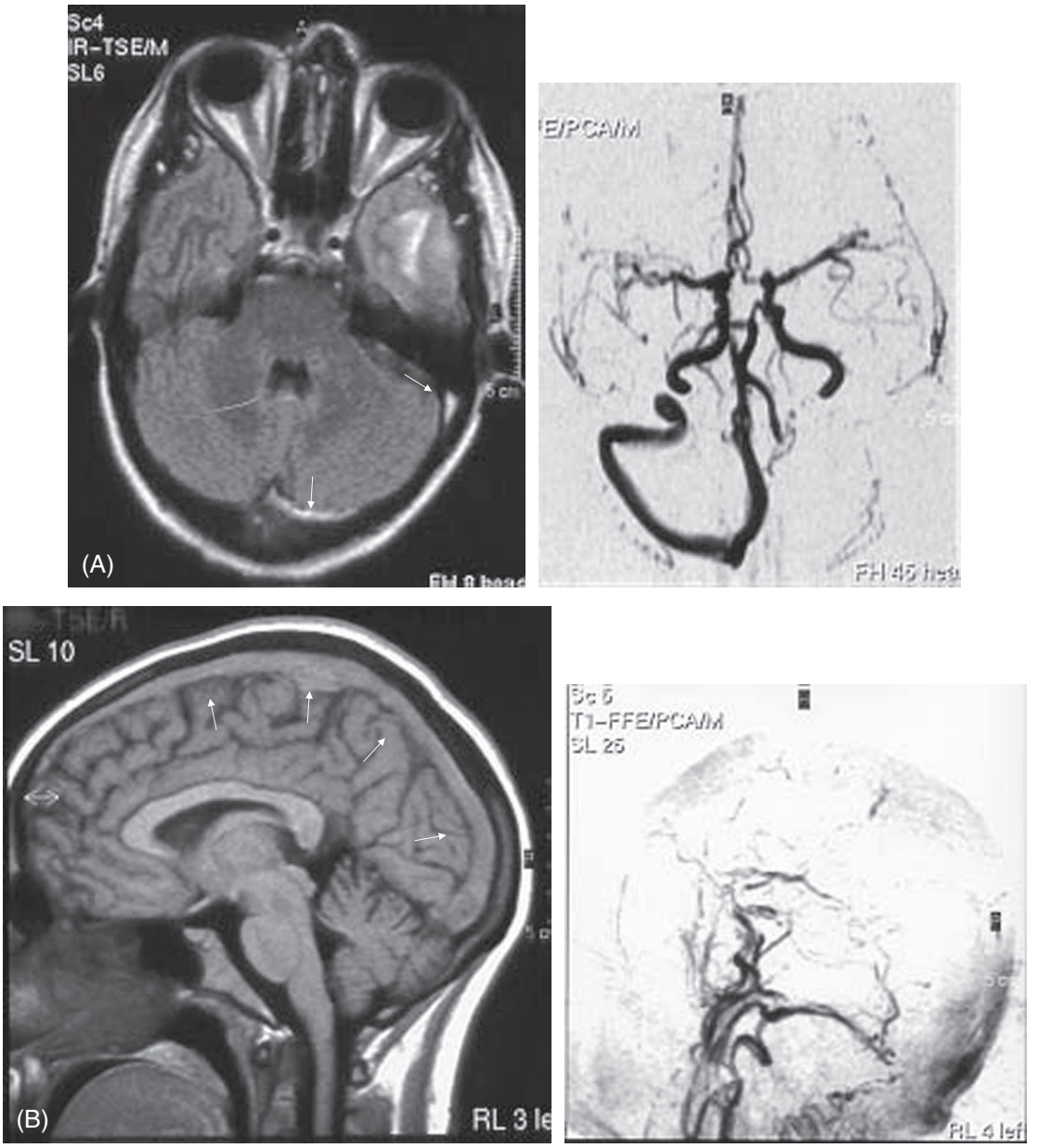

Fig. 40.4. Magnetic resonance imaging of sinus thrombosis. (A) T2-weighted MRI. Increased signal in left lateral sinus (arrows), with a left temporal lesion. Magnetic resonance venogram confirms the absence of signal in the left lateral sinus and normal flow in the remaining sinus. (B) T1-weighted MRI provides a sagittal view of an isointense signal in the thrombosed superior sagittal sinus (arrows). Magnetic resonance venogram confirms the absence of signal in the superior sagittal sinus and the deep cerebral venous system.

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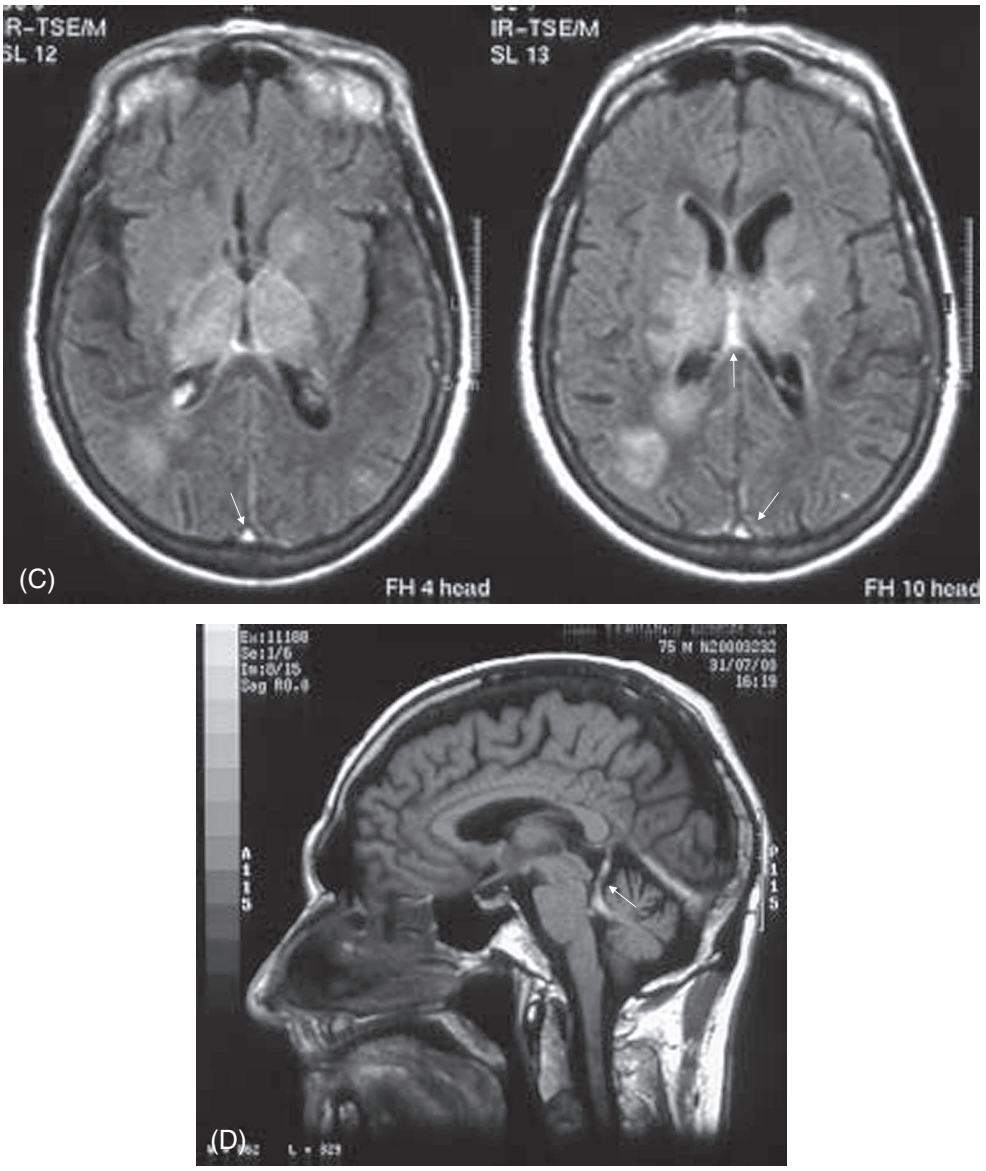

Fig. 40.4. Cont'd. (C) T2-weighted MRI shows bilateral thalamic edema due to thrombosis of the deep cerebral venous system (hyperintense signal in arrows) and cortico-subcortical right parieto-occipital oedema. It also shows a thrombus in the superior sagittal sinus as a hyperintense signal. (D) T1-weighted MRI depicts hyperintense signal in the thrombosed superior cerebellar vein.

and the sudden stop of cortical veins surrounded by dilated and tortuous collateral "corkscrew veins" (Fig. 40.5). Anatomical variations may complicate the interpretation of angiography, such as hypoplasia of the anterior part of the SSS, duplication of the SSS, and hypo- or aplasia of the transverse sinuses (Bousser and Russell, 1997). The interobserver agreement on CVT diagnosis is not perfect. The proportion of agreement is 62% for angiography and 94% for MR plus angiography (De Bruijn et al., 1998a).

Transcranial Doppler ultrasonography (Canhão et al., 1998; Valdueza et al., 1999) and transcranial power or color Doppler imaging, with or without the use of contrast (Becker et al., 1995; Ries et al., 1997; Stolz et al., 1999) were reported as potential non-invasive techniques for the diagnosis or follow-up of CVT, but more information is needed to determine the true clinical value of these methods.

Due to the high variability in clinical presentation, CVT is frequently suspected but its diagnosis requires neuroimaging investigations, which are not always immediately accessible. It would, therefore, be of great practical interest to have a test easy to perform in emergency care that could confidently rule out CVT. The

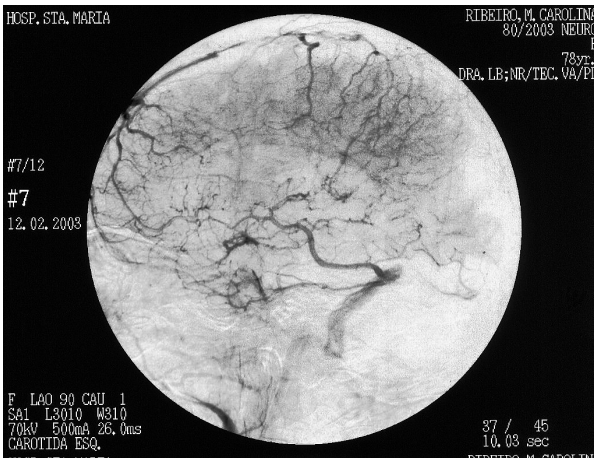

Fig. 40.5. Angiography of sinus thrombosis. In this angiogram (left lateral view) a large part of the superior sagittal sinus, the straight sinus and the deep venous system do not fill with contrast. Prominent collateral veins are shown.

D-dimer measurement may be useful in excluding CVT (Tardy et al., 2002; Lalive et al., 2003; Kosinski et al., 2004). However, CVT patients presenting with isolated headache may have normal D-dimer levels (Crassard et al., 2005).

40.7. Etiology

Many causes or predisposing conditions are associated with CVT (Table 40.1). In more than 85% of patients at least one risk factor can be identified (Ferro et al., 2004). As it is well established regarding venous thrombosis in other parts of the body, multiple risk factors may be found in about half of all patients (Ferro et al., 2004). The more frequent risk factors are prothrombotic conditions, either genetic or acquired, oral contraceptives, puerperium or pregnancy, malignancy, and infection (Ferro et al., 2004). Infective causes have declined and are responsible for 6–12% in large series of adults with CVT (Bousser and Russell, 1997; Ferro et al., 2004). In the ISCVT cohort, a prothrombotic condition was identified in 34% of the patients, being genetically determined in 22% of the patients. The genetic background probably determines the inherent individual risk. In the presence of some identified prothrombotic conditions e.g., antithrombine deficiency (Bousser and Russell, 1997), protein C or protein S deficiency (Enevoldson and Russell, 1990; Deschiens et al., 1996; DeVeber et al., 2001), factor V Leiden mutation (Ludemann et al., 1998; Martinelli et al., 1998; Weih et al., 2000), prothrombin gene mutation (Biousse et al., 1998; Martinelli et al., 1998; Reuner et al., 1998; Weih et al., 2000), hyperhomocysteinemia due to gene mutations in methylene tetrahydrofolate reductase (Hillier

Table 40.1

Risk factors associated with cerebral vein and dural sinus thrombosis

Genetic prothrombotic condition
Protein S, protein C and antithrombin III deficiency
Factor V Leiden mutation
Prothrombin gene mutation
Hyperhomocysteinemia caused by gene mutations in methylene tetrahydrofolate reductase
Acquired prothrombotic condition
Antiphospholipid antibody
Nephrotic syndrome
Hyperhomocysteinemia
Infection
Central nervous system
Ear, sinus, mouth, face, and neck
Systemic infectious disease
Inflammatory diseases
Systemic lupus erythematosus
Behçet's disease
Wegener's granulomatosis
Tromboangeitis obliterans
Inflammatory bowel disease
Sarcoidosis
Malignancy
Central nervous system
Solid tumor outside central nervous system
Hematological
Hematological condition
Polycythemia, thrombocytemia
Anemia, including paroxysmal nocturnal hemoglobinuria
Pregnancy and puerperium
CNS disorders
Dural fistulae
Other disorders
Dehydration
Congenital heart disease
Thyroid disease
Mechanical precipitants
Head injury
Lumbar puncture
Neurosurgical procedures
Jugular catheter occlusion
Drugs
Oral contraceptives
Hormone replacement therapy
Androgens
Asparaginase
Tamoxyfen
Steroids

et al., 1998; Cantu et al., 2004), patients are at increased risk of developing a CVT when exposed to head trauma, lumbar puncture, pregnancy, surgery, infection, and drugs.

The risk factors of CVT vary throughout life. In the Canadian Pediatric Ischemic Stroke Study Group, a risk factor was identified in 98% of the children (DeVeber et al., 2001). A prothrombotic state was found in 41% of the patients, most often in non-neonates. In neonates, acute systemic illness such as peri-natal complications and dehydration were frequent, occurring in 84% of patients (DeVeber et al., 2001). Head and neck disorders, mostly infections, and chronic systemic diseases (e.g., connective-tissue disease, hematologic disorder, and cancer) were common in non-neonate children.

The most frequent risk factor in young women is oral contraceptive use. Two case-control studies have shown an increased risk of sinus thrombosis in women who use oral contraceptives (De Bruijn et al., 1998b; Martinelli et al., 1998). The risk for women using oral contraceptives and also carrying a prothrombotic defect is increased compared with women without such risk factors (De Bruijn et al., 1998b).

In elderly CVT patients the proportion of cases without identified risk factors is high (37%). The most common risk factors are genetic or acquired thrombophilia, malignancies, and hematological disorders such as polycythemia (Ferro et al., 2005a). In almost 13% of adult CVT patients extensive search reveals no underlying cause. Sometimes, the cause (e.g., vasculitis, malignancy) is revealed only weeks or months after the acute phase.

40.8. Prognosis

Until recently the prognosis of CVT was considered unpredictable and often ominous (Bousser and Russell, 1997). Several recent prospective series, in particular the larger ISCVT cohort (Rondepierre et al., 1995; Preter et al., 1996; de Bruijn et al., 2001; Ferro et al., 2002, 2004; Breteau et al., 2003; Cakmak et al., 2003), confidently established the current vital and functional prognosis of patients with acute CVT (Table 40.2), with a 15% overall death or dependency rate. Predictors of poor long-term prognosis are CNS infection, malignancy, deep cerebral venous system thrombosis, hemorrhage on CT/MR, GCS score on admission <9, mental status disorder, age >37 years, and male gender. This predictive model was derived from the ISCVT cohort (Ferro et al., 2004) and was validated in other cohorts (Ferro et al., 2005c).

Despite the overall favorable prognosis, 4% of CVT patients die in the acute phase. Predictors of mortality at 30 days are depressed consciousness, mental status disorder, thrombosis of the deep cerebral venous system, right hemispherical hemorrhage and posterior fossa lesions (Canhão et al., 2005b). The main cause of death is transtentorial herniation secondary to a large hemorrhagic lesion (Canhão et al., 2005b). Other causes of death are herniation due to multiple lesions or to diffuse brain edema, status epilepticus, medical complications and pulmonary embolism (Diaz et al., 1992).

About one-quarter of the patients will deteriorate after admission. Neurological worsening may occur several days after admission, and may include depressed consciousness, mental state disturbance, new seizures, worsening of a previous symptom or a new focal deficit, increase in headache severity or visual loss. If neuroimaging is repeated, about one-third of such patients will show new parenchymal lesions (Crassard et al., 2003). Patients with depressed consciousness on admission are more likely to deteriorate and those with seizures at onset are more likely to have repeated seizures.

Table 40.2

Death or dependency at the end of the follow-up: data from prospective studies with long-term follow-up

Study	Follow-up	Death/dependency Yes/no	%	95% CI	Weight %
Rondepierre	6	8/10	44.4	24.6–66.3	1.9
Preter	78	18/67	21.2	13.8–31.0	9.1
De Bruijn	19	11/44	20.0	11.6–32.4	5.9
VENOPORT	22	8/83	8.8	4.5–16.4	9.7
Breteau	36	10/45	18.2	10.2–30.3	5.9
Cakmak	3	2/14	12.5	3.5–36.0	1.7
ISCVT	18	84/532	13.6	11.2–16.6	65.8
Total		141/795	15.1	12.9–17.5	100.0

Test for heterogeneity. $\chi^2 = 30.04$; df = G; $p < 0.00001$.

Recanalization occurs in 40–90% of patients depending on the occluded sinus (less often in the lateral sinus), mostly within the first 4 months (Baumgartner et al., 2003). Recanalization of the occluded sinus is not related to outcome (Strupp et al., 2002). The presence of hyperintensities in the veins/sinus in diffusion-weighted MRI predicts low recanalization rate (Favrole et al., 2004).

CVT patients who survive the acute phase are at risk of a number of complications. The underlying disease may lead to death. Recurrent CVT is very rare and also difficult to document, in particular if a previous follow-up MRI/MR angiography is not available. Other thrombotic events, in particular deep venous thrombosis on the limbs or pelvis and pulmonary embolism, occur in up to 5% of the patients. Seizures occur in 11% of the patients, more so if the patient had seizures during the acute phase, a hemorrhagic parenchymal lesion or a motor deficit. Headaches severe enough to require bed rest or hospital admission afflict 14% of the patients. Severe visual loss due to intracranial hypertension is fortunately a very rare event nowadays (Purvin et al., 1995; Ferro et al., 2002, 2004).

Despite the apparent general good recovery half of the survivors of CVT feel depressed or anxious (Madureira et al., 2001) and minor cognitive or language deficits (Buccino et al., 2003) may preclude that they resume their previous level of professional activity (de Bruijn et al., 2000).

As pregnancy and puerperium are risk factors for CVT, an important question is the risk of future pregnancies in women who have had a CVT. At least six studies have addressed this issue (Srinivasan, 1983; Preter et al., 1996; Lamy et al., 2000; Ferro et al., 2002, 2004; Mehraein et al., 2003) with a total of 855 women under observation, of whom 83 became pregnant after their CVT (101 pregnancies). Eighty-eight percent of the pregnancies ended in a normal birth, the remaining being prematurely terminated by voluntary or by spontaneous abortion. There were no instances of recurrent CVT and only two cases of deep venous thrombosis.

40.9. Treatment

40.9.1. General measures

The therapeutic priorities in the acute phase are to stabilize the patient, prevent new infarcts, prevent or reverse herniation, and treat seizures. Vasogenic edema occurs in acute CVT (Chu et al., 2001) and treatment with mannitol can help to reduce intracranial hypertension and brain shift in severe cases. In patients with impending herniation, hemicraniectomy can be life-saving (Stefini et al., 1999). Since about 40% of all patients with CVT have seizures in the acute phase, prophylactic anti-epileptic treatment should be prescribed in patients with early acute seizures and supratentorial lesions (Ferro et al., 2001). Regional infections that may have caused CVT must be diagnosed and treated.

40.9.2. Heparin

Heparin is the obvious treatment for any venous thrombosis, and also for CVT. Yet, anticoagulant treatment has been controversial due to the high incidence of spontaneously hemorrhagic infarcts (about 40%) in patients with CVT. Heparin might cause venous infarcts to become hemorrhagic, or increase bleeding in already hemorrhagic lesions. New or increased hemorrhage does indeed occur after heparin treatment for CVT, but the frequency is low. In one study new intracranial hemorrhages occurred in 4 of the 112 (3.6%) patients with sinus thrombosis treated with anticoagulants. However, in patients who did not receive anticoagulants, new hemorrhages were more frequent (2/30, 6.7%) (Ferro et al., 2001). Another study reported 3 new hemorrhages in 56 patients (5.4%) treated with intravenous heparin (Einhäupl et al., 1991). Other non-controlled studies have reported that the outcome after cerebral sinus thrombosis improved with anticoagulant treatment, without hemorrhagic complications (Bousser et al., 1985; Ameri and Bousser, 1992; Brucker et al., 1998; Ferro et al., 2001). The first placebo-controlled clinical trial of (intravenous) heparin in CVT (Einhäupl et al., 1991) was stopped after 20 patients were included (10 heparin, 10 placebo) because the investigators found a statistically significant effect. In the placebo group three patients died, six survived with minor deficits and one recovered completely. In the heparin group two patients had minor deficits and eight recovered completely. The interpretation of these results is controversial. Analysis of this trial according to the standard methods used in the Cochrane reviews gives a statistically non-significant difference between heparin and placebo (Stam et al., 2002).

Another randomized trial, published in 1999, examined subcutaneous low-molecular weight heparin (nadroparin) in a therapeutic dose, compared to placebo (De Bruijn et al., 1999). This trial included 60 patients (30 in each group). After 12 weeks, 4 out of 30 patients (13%) in the nadroparin group were dead or dependent, in the placebo group this was 6 out of 29 (21%; $p = 0.51$). Both trials included patients with hemorrhagic infarcts on their baseline scans, but there were no intracranial hemorrhagic complications. Interestingly, both trials report one case of pulmonary embolism that occurred in the placebo groups.

The third trial included 57 women with puerperal CVT in India (Nagaraja et al., 1995). The diagnosis was not confirmed by angiography or MRI/MRA. Patients with hemorrhage on their CT scan were excluded. Initial treatment was with intravenous unfractionated heparin, 5000 IU every 6 hours. Assessment was non-blinded. In the heparin group all 29 patients recovered. Two patients in the control group died, and one had a residual paresis at 6 months (difference not statistically significant).

In a Cochrane review only the two first trials were included (Stam et al., 2002). The meta-analysis shows a relative risk of 0.46 (95% CI, 0.16–1.31) of death or dependency after anticoagulant therapy as compared to placebo, a non-significant trend in favor of heparin. Although the trials do not unequivocally show a benefit of heparin, all three trials show a slight advantage of heparin compared to placebo. In addition, the relative safety of heparin in sinus thrombosis was confirmed, and in the placebo groups two cases of pulmonary embolism occurred. These findings support the choice of full anticoagulation with heparin (intravenous, or subcutaneous high-dose low-molecular weight) as the initial treatment for nearly all patients with (sub-)acute sinus thrombosis.

40.9.3. Thrombolysis

Endovascular thrombolysis, with or without mechanical thrombus disruption, has some theoretical advantages over heparin treatment, the most important being that, if successful, the bulk of the thrombotic material can be removed from the major sinuses within hours. There are however significant problems. The procedure is complicated and expensive. Patients need anesthesia and intensive care monitoring, and usually the catheter remains in the sinus for hours to days, with repeated applications of the thrombolytic agent and radiological assessments. Usually, only one transverse sinus, the superior sagittal sinus, and sometimes the straight sinus can be entered. Finally, there is always the concern that venous infarcts in CVT become hemorrhagic after thrombolytic treatment.

No randomized trials of endovascular treatment for sinus thrombosis have been done. Canhão et al. summarized the non-randomized evidence up to 2001 (Canhão et al., 2003). They reported new symptomatic intracranial hemorrhages in 5% of the patients and a poor outcome in 13% of the published cases (mortality 9%, dependency 4%). This is in the same range as the results obtained in the trials with heparin and large international prospective cohort study (Ferro et al., 2004) although more severe cases seem to have been selected for endovascular treatment. On the other hand, publication bias may have favored the reports (all case reports and small series) with better results. Therefore, a randomized trial to compare endovascular treatment with heparin is needed. For now, local thrombolysis should be restricted to patients with a poor prognosis, and to centers with expertise in interventional radiology.

40.9.4. Oral anticoagulants

There is no published evidence on how long patients should continue with oral anticoagulant treatment after CVT. A too-brief period of anticoagulation carries the risk of recurrent CVT. An increased rate of bleeding is inevitable with longer anticoagulant treatment. Usually, treatment with vitamin K antagonists, aiming at an international normalized ratio (INR) between 2 and 3.5, is given for 6–12 months to patients without known risk factors. In patients with inherited or acquired thrombophilia we follow the recommendations of Middeldorp et al. (2000). After the first thrombotic episode we give warfarin for 1 year; thereafter they need anticoagulant protection in high-risk situations (surgery, trauma, immobilization, pregnancy, post-partum). Oral contraception containing estrogens should be avoided by those patients, since they are associated with an increased risk of CVT (De Bruijn et al., 1998b).

40.9.5. Intracranial hypertension

In patients with only symptoms of chronic (more than about 3 weeks) intracranial hypertension, the therapeutic priority is to lower the intracranial pressure. This will reduce headache and papilledema. The first thing to do is a lumbar puncture and measure the cerebrospinal fluid pressure, after excluding intracranial lesions. If the pressure is not controlled after one or two lumbar punctures, we start acetazolamide, 250 mg twice daily. Patients who cannot tolerate acetazolamide may occasionally respond to furosemide. Corticosteroids may theoretically have a beneficial effect, by reducing vasogenic edema (Corvol et al., 1998). A case-control study showed that steroids in the acute phase of CVT did not improve outcome (Canhão et al., 2008).

Repeated lumbar punctures may be needed to prevent visual loss. An external lumbar drain may be applied for a couple of days. If all these measures do not control the intracranial pressure a lumboperitoneal or ventriculocardial shunt is needed. Fenestration of the optic nerve sheet should be considered in patients with papilledema and progressive visual loss (Tse and Chang, 1999). Hemicraniectomy may be life-saving in patients with parenchymal lesions producing impeding herniation (Keller et al., 2005).

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Chapter 41

Illicit drug use/abuse and stroke

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41.1. Introduction

The problem of drug use and abuse has reached national and international proportions, with a significant impact on public health and social welfare. Toxicity to every major organ system in adults as well as to the fetus from illicit drug use has been noted (Cregler and Mark, 1986; Kloner et al., 1992; Volpe, 1992; Sloan et al., 1998a). The diverse neurologic consequences of drug use are summarized elsewhere (Brust, 2004). Over the last 60 years, a large number of case reports, letters to the editor, case series, autopsies, and epidemiologic studies from around the world have reported the occurrence of cerebrovascular symptoms in association with illicit drug use. These studies, as well as review articles (as summarized in Sloan, 1993; Sloan et al., 1998a; Brust, 2004; Williams, 2004) report all subtypes of transient and permanent ischemic events in the retinal, anterior, and posterior circulations, as well as various causes of intracerebral and subarachnoid hemorrhage (Caplan, 1994; Sloan et al., 1998a). More recently, it has been emphasized that chronic cocaine use is associated with abnormal white matter signals suggestive of subclinical vascular events on MRI (Bartzokis et al., 1999), cerebral atrophy (Pascaul-Leone et al., 1991), mild cognitive impairment (Ardila, 1991; Weinreib et al., 1993; Pascaul-Leone et al., 1990), and reduced frontal white matter integrity on diffusion tensor imaging (Lim et al., 2002). Use of heroin may be associated with acute cerebrovascular or spinal vascular disease. Other drugs associated with acute cerebrovascular diseaseinclude other narcotics, cocaine, amphetamines, over-the-counter (OTC) sympathomimetic decongestants, cold remedies and diet aides, lysergic acid diethylamide (LSD), phencyclidine (PCP), marijuana, and Ecstasy. Stroke related to use of "ice" (smoked crystallined-amphetamine), 3,4-methylenedioxy amphetamine (MDA), and 3,4-methylenedioxy methamphetamine (MDMA) have been rarely observed. Among the OTC sympathomimetic agents, both phenylpropanolamine and ephedrine have been removed from the market due to safety considerations. A brief history of the relationship between illicit drug use/abuse and stroke is shown in Table 41.1. Specific drugs associated with stroke are listed in Table 41.2.

41.2. Epidemiologic considerations of drug abuse and stroke

Evidence is accumulating to define the strength of association between illicit drug use/abuse and stroke, including ischemic stroke, intracerebral hemorrhage and subarachnoid hemorrhage. Many studies of stroke in young adults in the 1970s, 1980s, and 1990s (as reviewed in Sloan et al., 1998a) revealed that 0–6% of strokes were associated with illicit drugs. A number of case series and single hospital- or population- based case-control studies of the relation between illicit drug abuse and stroke are now available (Table 41.3). More recently published studies performed during the US cocaine epidemic were carried out in a handful of US centers and used a variety of methodologies. One retrospective single hospital-based study (Kaku and Lowenstein, 1990) observed that 73 of 214 (34.1%) young adult stroke patients (15–44 years old) admitted to San Francisco General Hospital between 1979 and 1988 had histories of recreational drug use (most frequently cocaine) recorded in the chart. A prospective single hospital-based study (Sloan et al., 1991) evaluated 167 consecutive stroke patients admitted to the University of Maryland Hospital between September 1, 1988 and August 1, 1989 and found that 7 of 51 (13.7%) patients aged 15–49 years (average 41 years) had used a variety of illicit drugs.

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Table 41.1

Stroke and illicit drug use: historic perspectives

1945	Amphetamine overdose, subdural/intracerebral hematoma, and death
1965	Combined amphetamine and monoamine oxidase inhibitor use, intracerebral hemorrhage, and death
1968	Stroke linked to heroin addiction
1970	Demonstration of necrotizing angiitis in polysubstance intravenous drug users with cerebral infarction and hemorrhage
l97l–1990s	Induction of vasospasm/vasculitis in experimental animals
1970s	Initial reports of ischemic stroke and hemorrhagic stroke with amphetamines. cocaine, lysergic acid diethylamide, and phencyclidine
1980s	US "crack" cocaine epidemic; increasing frequency of ischemic and hemorrhagic stroke related to crack, powder, and intravenous cocaine use
1990s	Case series of cocaine-related stroke: observational studies of stroke and illicit drug use
1990s–2000s	Case control studies, both population- and hospital-based, showing strength of association between illicit drug use and stroke

Table 41.2

Drugs associated with stroke

Drug
Heroin
Paregoric
Meperidine
Hydromorphone (Dilaudid)
Pentazocine-tripelennamine (Ts and Blues)
Cocaine
Dextroamphetamine
Methamphetamine
Methylphenidate (Ritalin)
Amphetamine (Benzedrine)
Ecstasy
Ice (smoked crystalline *d*-methamphetamine)
3,4-methylenedioxy amphetamine (MDA)
3,4-methylenedioxy metamphetamine (MDMA)
Phenyl/propanolamine (PPA)
Ephedrine (EPH)
Pseudoephedrine (PSE)
Diethylpropion hydrochloride
Phentermine
Phendimetrazine
Fenfluramine
Lysergic acid diethylamide (LSD)
Phencyclidine (PCP)
Marijuana

A retrospective study (Mitsias et al., 1992) of consecutive ischemic stroke patients less than 50 years old admitted to Henry Ford Hospital between April 1989 and July 1991 found that 16 of 56 (29%) were recreational drug users. A large retrospective population-based study of ischemic stroke patients aged 15–44 years at 46 hospitals in the Baltimore–Washington area in 1988 and 1991 (Kittner et al., 1998; Sloan et al., 1998b) found that 51 of 422 (12.1%) showed evidence of illicit drug use within 48 hours of ischemic stroke onset. Patients with drug use were more likely than other stroke patients to be black ($p = 0.01$), aged 25–39 years ($p = 0.004$), and be smokers ($p = 0.006$), and were less likely to have hypertension ($p = 0.004$) and diabetes mellitus ($p = 0.004$). A retrospective study of 112 young adult ischemic stroke patients admitted to Grady Memorial Hospital in Atlanta between January 1, 1990 and June 30, 1994 (Qureshi et al., 1995) found that 30 (26.8%) had a history of cocaine use; seven (6%) ischemic strokes were attributed to cocaine use.

One retrospective study using a statewide administrative database (Chyatte et al., 1992) analyzed 48,844 hospital discharges with stroke as a primary diagnosis (*International Classification of Diseases*, 9th edn; code numbers 430–438) in Connecticut during 1981, 1983, 1985, 1987, 1988, and 1989. Intracerebral hemorrhage cases increased significantly from 376 in 1981 to 604 in 1989 ($p = 0.005$). Although the authors believed that the increased incidence could be due to identification of milder cases, 10 of 17 (59%) tested patients in 1989 to 1990 had positive toxicology screens for cocaine or cocaine metabolite. A large retrospective population-based study of intracerebral/intraventricular hemorrhage patients aged 15–44 years at 46 hospitals in the Baltimore–Washington area in 1988 and 1991 (Sloan et al., 1996) found that 26 of 195 (13.3%) showed evidence of illicit drug use within 48 hours of intracerebral/intraventricular hemorrhage onset. There was a highly significant increase in the detection of recent illicit drug use from 1988 (8%) to 1991 (23%), $p = 0.007$. Recent illicit drug-associated intracerebral/intraventricular hemorrhage patients in 1991 were more likely than

Table 41.3

Association between illicit drug use and stroke

Author Case series	Years of study	Age group (years)	Any stroke *n*/*N*(%)	IS *n*/*N*(%)	ICH *n*/*N*(%)	SAH *n*/*N*(%)
Kaku	1979–1988	15–44	73/214 (34)			
Sloan	1988–1989	15–49	7/51 (13.7)			4/26(15.4)
Mitsias	1989–1991		16/51 (29)			
Adams	1987–1993	15–45		7/321 (2.1)		
Sloan/BWYSSG	1988, 1991	15–45		51/422 (12.1)	26/195 (13.3)	
Qureshi	1990–1994	15–45			18/67 (27)	11/38 (29)
Simpson	1980s					17/150 (11.3)
Case Control Studies (OR, 95% CI)						
Kaku	1979–1988	15–44	6.5 (3.1–13.6)			
		< 35	11.2 (3.2–42.5)			
	Stroke within 6 hours		49.4 (6.4–379)			
Qureshi ("crack")	1994–1996		1.9 (0.7–5.1)	1.2 (0.4–3.8)		
Sloan (cocaine)	1992–1996	18–65	1.83 (0.95–3.8)	1.92 (0.59–6.3)	2.96 (1.35–6.5)	0.56 (0.18–1.76)
	(Marijuana)		1.38 (0.73–2.61)	1.19 (0.51–2.8)	1.16 (0.46–2.93)	1.63 (0.7–3.82)
Sloan/BWYSSG	1992–1996	15–44				
	Current cocaine			3.4 (1.4–8.3)		
	Cocaine within 24 hours			Infinity (2.6–infinity)		
Pettiti/KP	1991–1994					
	Cocaine or amphetamine		7.0 (2.8–17.9)			
	Cocaine—any		13.9 (2.8–69.4)			
	Cocaine—powder/paste		19.7 (2.3–166.3)			
	Cocaine—"crack"		11.2 (1.1–118.8)			
	Amphetamine		3.8 (1.2–12.6)			
HSP	1994–1999	15–49		NS	(3.95–infinity)	24.97

BWYSSG = Baltimore–Washington Cooperative Young Stroke Study Group; 95% CI = 95% confidence interval; HSP = Hemorrhagic Stroke Project; ICH = intracerebral hemorrhage; IS = ischemic stroke; KP = Kaiser-Permanente project; *n* = number of drug-associated cases; *N* = total number of cases; OR = odds ratio; SAH = subarachnoid hemorrhage.

other intracerebral/intraventricular hemorrhage patients in 1991 to be black ($p<0.001$) and smokers ($p=0.003$), but were similar with respect to age, hypertension, and diabetes mellitus. A retrospective study of 67 young adult intracerebral hemorrhage patients admitted to Grady Memorial Hospital between January 1, 1990 and June 30, 1994 (Qureshi et al., 1995) found that 18 (27%) had a history of cocaine use. In the Hemorrhagic Stroke Project involving 44 hospitals in 6 states in the USA from 1994 to 1999 (Feldmann et al., 2005), 4 of 217 (2%) of intracerebral hemorrhage patients aged 18–49 showed evidence of cocaine use.

A prospective single hospital-based study (Sloan et al., 1991) found that 4 of 26 (15.4%) subarachnoid hemorrhage patients with complete historic information (3 aneurysmal, 1 arteriovenous malformation) had used illicit drugs. A retrospective large single-hospital study (Simpson et al., 1990, 1991) observed that 17/150 (11.3%) patients with subarachnoid hemorrhage (16 aneurysmal, 1 arteriovenous malformation) were intravenous drug users. A retrospective study (Oyesiku et al., 1993) of 12 cocaine-related subarachnoid hemorrhage patients admitted to Grady Memorial Hospital in Atlanta between 1988 and 1990 noted that 10 (84.9%) were related to aneurysm rupture, suggesting that cocaine use may be a negative factor in the natural history of intracranial aneurysms. A more recent retrospective study of 38 young adult subarachnoid hemorrhage patients admitted to Grady Memorial Hospital between January 1, 1990 and June

30, 1994 (Qureshi et al., 1995) found a history of cocaine use in 11 patients (28.9%). In the Hemorrhagic Stroke Project involving 44 hospitals in 6 states in the USA from 1994 to 1999 (Broderick et al., 2003), 9 of 312 (3%) of subarachnoid hemorrhage patients aged 18–49 showed evidence of cocaine use.

Recent case control studies have clarified the relationship between illicit drug use and stroke. One retrospective single hospital-based case-control study (Kaku and Lowenstein, 1990) of young adult stroke patients (15–44 years) used control subjects matched for age (±3 years), gender, and year of hospital discharge that were selected from patients with acute asthma exacerbation (81.4%), appendicitis (12.1%), and cholecystitis (6.5%) who had clear documentation of the presence or absence of drug abuse in the chart. Predisposing factors for stroke were found in 93% of stroke patients and 63% of controls. After controlling for identifiable risk factors (cardiac disease, diabetes mellitus, hypertension, smoking, alcohol use, and pregnancy) and excluding endocarditis cases, the estimated relative risk (RR) for stroke among drug users compared with non-drug users was 6.5 (95% CI = 3.1–13.6). Among patients less than 35 years old, the RR for stroke was 11.2 (95% CI = 3.2–42.5). Separate analyses for specific stroke subtypes were not reported. A significant increase was found in the overall proportion of drug users among young stroke patients between 1979 and 1985 (26%), and 1986 and 1988 (46%), $p = 0.003$. A single hospital-based study of "crack" cocaine use in patients aged 20–39 years (Qureshi et al., 1997) found no significant increase in the risk for any stroke (OR = 1.9, 95% CI = 0.7–5.1) or ischemic stroke (OR = 1.2, 95% CI = 0.4–3.8). Another single hospital-based study (Sloan et al., 1998c) found a significant association between current cocaine use and intracerebral hemorrhage (OR = 2.96, 95% CI = 1.35–6.5), but not with any stroke (OR = 1.83, 95% CI = 0.95–3.8), ischemic stroke (OR = 1.92, 95% CI = 0.59–6.3) or subarachnoid hemorrhage (OR = 0.56, 95% CI = 0.18–1.76). The same investigators (Sloan et al., 1999) also found that current marijuana use did not increase the risk of all stroke or any stroke subtype.

In the population-based Stroke Prevention in Young Women study (Sloan et al., 1997), the age-adjusted risk of ischemic stroke with current (within 30 days) cocaine use was OR = 3.4 (95% CI = 1.4–8.3) and risk of cocaine use within 24 hours of ischemic stroke onset was OR = infinity (8 cases, 0 controls, 95% CI = 2.6–infinity, $p = 0.001$). The risk of ischemic stroke from current cocaine use after adjustment for age and cerebrovascular risk factors was OR = 2.0 (95% CI = 0.7–5.8), with confounding resulting from current smoking and hypertension. The population-based Kaiser Permanente study (Pettiti et al., 1998) showed that after adjustment for cerebrovascular risk factors, use of cocaine or amphetamine in young women was associated with a significant increase in stroke risk (OR = 7.0, 95% CI = 2.8–17.9). The effects were stronger for any cocaine (OR = 13.9, 95% CI = 2.8–69.4) than for amphetamine (OR = 3.8, 95% CI = 1.2–12.6). In patients aged 18–49 years from 44 hospitals from 6 US states involved in the Hemorrhagic Stroke Project (Feldmann et al., 2005), cocaine use was not independently associated with intracerebral hemorrhage. However, the Hemorrhagic Stroke Project (Broderick et al., 2003) found that cocaine use within 3 days of onset of subarachnoid hemorrhage (3% cases, 0% controls) was associated with a marked increase in risk (bivariate OR = 24.97, 95% CI = 3.95–infinity, adjusted estimate not calculable).

In the aforementioned case-control studies, the stroke risk for cocaine use varies widely. One single-hospital case-control study (Magder et al., 2000) using a statistical method incorporating multiple imperfect sources of information regarding cocaine use (structured interview, toxicological screen, chart review) showed that the OR for the risk of any stroke with cocaine use may vary from 1.59 to 2.35, depending on the sensitivity and specificity of the information source and whether the assumption of conditional independence of information sources was satisfied. The varying estimates of stroke risk attributable to cocaine use may in part be explained by the greater prevalence of drug use in urban inner city hospitals with resultant lower risk estimates than in population-based studies, ascertainment bias in population-based controls, selection of controls, and other factors.

These observed associations must be viewed in the context of the risk of stroke due to alcohol use. A review article (Camargo, 1989) and meta-analysis of 19 cohort studies and 16 case-control studies (Reynolds et al., 2003) have summarized the epidemiological associations between alcohol and stroke. Compared with abstainers, ingestion of more than 60 g of alcohol (five drinks) per day is associated with an increased overall risk of total stroke (RR = 1.64, 95% CI = 1.39–1.93), ischemic stroke (RR = 1.69, 95% CI = 1.34–2.15), and hemorrhagic stroke (RR = 2.18, 95% CI = 1.48–3.20); less than 12 g of alcohol per day is associated with reduced risk of total stroke (RR = 0.83, 95% CI = 0.75–0.91) and ischemic stroke (RR = 0.80, 95% CI = 0.67–0.96); and 12–24 g of alcohol per day is associated with reduced risk of ischemic stroke (RR = 0.72, 95% CI = 0.57–0.91). Results are similar for more than 60 g per day by gender (men: RR = 1.76,

95% CI = 1.57–1.98; women: RR = 4.29, 95% CI = 1.30–14.14) and for study design (cohort: RR = 1.63, 95% CI = 1.49–1.79; case-control: RR = 1.98, 95% CI = 1.35–2.92).

41.3. Pathophysiologic effects of drug use

41.3.1. Pharmacologic and cardiovascular effects

The mechanism(s) by which the various drugs produce acute cardiovascular and cerebrovascular disease may be explained in part by their pharmacologic effects on neurotransmitters and physiologic actions. Most of these compounds (heroin, cocaine, amphetamines, OTC sympathomimetics, PCP, LSD) gain entry into the central nervous system and have a variety of effects on neurotransmitters. Many drugs increase catecholamine release from central noradrenergic nerve terminals (amphetamines, OTC sympathomimetics), block reuptake of catecholamines into nerve terminals (cocaine, PCP), or increase plasma catecholamine levels (ethanol, cocaine, tripelennamine and pentazocine) ("Ts and Blues"). Sometimes similar effects on central serotonergic and dopaminergic neurotransmission (amphetamine, cocaine, and PCP) are observed. Ts and Blues and PCP may antagonize central cholinergic function. LSD appears to act as an agonist at serotonergic receptors, either pre- or post-synaptically (Brust, 2004). For the OTC sympathomimetics, compounds devoid of -OH groups tend to cross the blood–brain barrier and have enhanced central nervous system activity. Substitution at the alpha-carbon blocks oxidation by monoamine oxidase (MAO), whereas beta-carbon substitution increases agonist activity at alpha- and beta-receptors and reduces central nervous system stimulant action. These structure–activity relationships explain why certain compounds are likely to have clinically important central nervous system effects (Weiner, 1980; Goodman et al., 1990) (Fig. 41.1).

With the exception of heroin and LSD, all drugs of interest may produce mild to profound blood pressure elevation, at times with bradycardia or tachycardia. Phencyclidine may produce a pressor response by directly stimulating alpha-adrenergic receptors. Peripheral vasoconstriction may occur with cocaine, amphetamines, or ephedrine. Experimental studies (as reviewed by Sloan et al., 1998a) indicate that cocaine may also potentiate responses to catecholamines by central mechanisms. Elevated catecholamine levels may predispose to cardiac arrhythmias. A variety of cardiac arrhythmias, such as atrial fibrillation and ventricular dysrhythmias, may be produced. Phencyclidine rarely produces tachycardia or cardiac arrest.

Only cocaine and ethanol are known to have effects on hemostasis. Experimental studies (as reviewed by Sloan et al., 1998a) show that cocaine may: enhance platelet aggregability, increase thromboxane B2 levels, increase the frequency of elevated baseline level of circulating activated platelets, produce a dose-related increase in levels of platelet alpha-granule release as indicated by increased expression of P-selectin (alpha-granule membrane protein), increase platelet-associated fibrinogen, and increase plasminogen activator inhibitor (PAI-1) activity. There is a great heterogeneity in platelet responses to cocaine. In one case of cocaine-related arterial thromboses, reversible depletion of protein C and antithrombin III was reported (Isner and Chokshi, 1991). The coexistence of other putative prothrombotic substances, such as anticardiolipin antibodies, has been infrequent (Levine et al., 1990). Ethanol may increase platelet aggregability, decrease fibrinolytic activity, decrease levels of factor VIII—related antigen and factor VIII ristocetin cofactor and shorten the bleeding time, thus leading to a prothrombotic state. On the other hand, ethanol may decrease circulating levels of hepatic clotting factors, enhance fibrinolysis, and lead to the production of abnormal fibrinogens and other coagulopathies, thus producing a hemorrhagic diathesis. Because patients tend to use more than one drug at the same time and have differing pre-morbid medical conditions and medication use, it is difficult to predict a priori the hemostatic consequences of drug use in an individual patient.

41.3.2. Vascular effects

Many drugs have effects on the peripheral and cerebral vasculature (as reviewed by Sloan et al., 1998a). Vasospasm may be produced by ethanol, cocaine, phenylpropanolamine, phentermine, and possibly phendimetrazine. Experimental and clinical studies suggest that cocaine may also act independently to produce vasoconstriction of vascular smooth muscle. Cocaine causes an increase in calcium levels and enhances spontaneous release of calcium from the sarcoplasmic reticulum. Pathologic changes consistent with disturbed calcium homeostasis (e.g., myocardial contraction bands) have been observed more frequently in the hearts of individuals who have died from acute cocaine toxicity compared with other drug-related deaths (Billman, 1990; Isner and Chokshi, 1990). In coronary arteries and coronary arterioles <65 μm in diameter, cocaine and norcocaine metabolites cause an endothelium-independent contractile process with a resultant decrease in coronary blood flow. These effects may be antagonized by the calcium antagonists

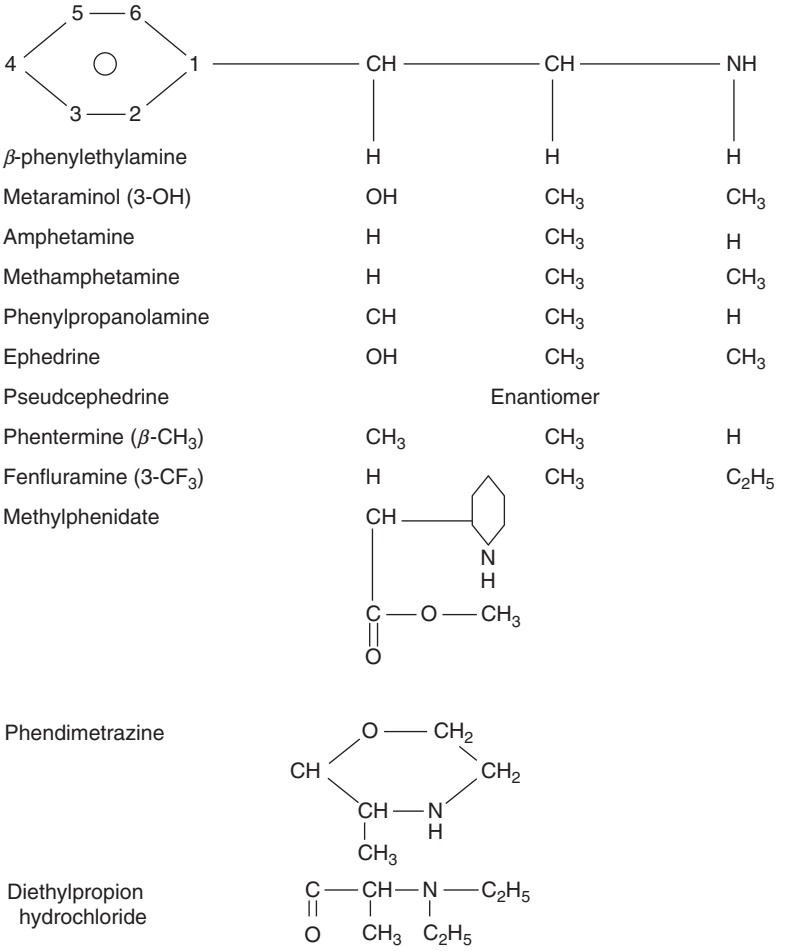

Fig. 41.1. Clinical structures of amphetamine and related sympathomimetic drugs. (Adapted by permission from Sloan MA. Cerebrovascular disorders associated with licit and illicit drugs. In: Fisher M, Bogousslavsky J, Eds. Current review of cerebrovascular disease. Philadelphia: Current Medicine, 1993: 48–62.)

diltiazem and nitrendipine. Experimental and clinical studies (as reviewed by Kloner et al., 1992; Sloan et al., 1998a) show that cocaine may induce vasoconstriction of normal coronary arteries or at sites of pre-existing atherosclerotic stenosis, as well as thrombosis, leading to myocardial ischemia and acute myocardial infarction. These disorders may lead to acute or chronic cardiomyopathy, the latter of which may be reversible or irreversible. Cocaine may also cause an acceleration of atherosclerosis, which may be enhanced by release of platelet-derived mitogens from alpha-granules in activated platelets.

Cocaine has multiple effects on the cerebral vasculature. Experimental and involved vessels include cortical pial arteries, arterioles, veins, and venules. Increasing concentrations of cocaine hydrochloride may cause vasospasm, rupture of capillaries and venules and microhemorrhages. The combination of high doses of cocaine and amphetamine may lead to severe vasospasm. More recently, dose-related cerebral vasoconstriction capable of causing ischemic stroke has been demonstrated in healthy young cocaine users (Kaufman et al., 1998). The effects of cocaine may be antagonized by verapamil and, in dose-dependent fashion, with the natural calcium antagonist magnesium. Cocaine may also cause small vessel arteritis (Krendel et al., 1990; Fredericks et al., 1991; Tapia et al., 1993) and microaneurysms (Nalls et al., 1989).

Experimental studies (as reviewed by Sloan et al., 1998a) have shown that other drugs have significant vasoactive effects. Phencyclidine, LSD, and mescaline can also produce a contractile response when directly applied to isolated brain arteries. Similar effects may be seen with amphetamines. Intrathecal norepinephrine may produce biphasic vasospasm that is morphologically similar to the vasculopathy seen after subarachnoid hemorrhage. Intravenous methamphetamine or methylphenidate (Ritalin) produces immediate (<10 min) decrease in vessel caliber,

vascular occlusion, subarachnoid hemorrhage with generalized vasospasm, multifocal infarction, edema, and petechial hemorrhages. In addition, microaneurysms similar to those seen in drug addicts with "necrotizing angiitis" (Rumbaugh et al., 1971) have been observed.

Inflammation of small-, medium-, and large-sized intracranial arteries, with beading of vessels of "arteritis," has been reported with abuse of heroin, Ts and Blues, various amphetamines, phentermine and phendimetrazine-containing diet pills, phenylpropanolamine (PPA), ephedrine (EPH), and pseudoephedrine (PSE). The necrotizing lesions seen in amphetamine abusers are similar to those seen with typical periarteritis nodosa (Citron et al., 1970). Immunologic aberrations or toxic effects may contribute to the pathogenesis of these vascular effects (see Sloan et al., 1998a for details). Hypergammaglobulinemia, circulating immune complexes, eosinophilia, positive direct Coombs' test, elevated erythrocyte sedimentation rate (ESR), antibodies to smooth muscle and lymphocyte membranes or thyroid microsomes, false-positive syphilis serology, lymph node hypertrophy, and hypersensitivity vasculitis on skin biopsy have been reported in users of heroin, phentermine/phendimetrazine, and EPH. Toxic effects of heroin and PPA may lead to segmental or multifocal vascular narrowing. Large vessel (extracranial and intracranial) stenotic or occlusive disease, such as progressive stenosis, occlusion, or small-branch occlusion, may be induced by heroin, cocaine, various amphetamines, and LSD. These findings may lead to stasis, hypoperfusion, or thrombo-embolism. It is not yet known whether cocaine can induce accelerated atherosclerosis in the extracranial or intracranial circulations. Cocaine use can lead to stroke with normal appearing arteries that are small or with unusual disruption of the internal elastic lamina. However, patients often use multiple drugs and ethanol, which tends to confound efforts to assign cause and effect to specific agents.

41.4. Clinical presentation

The general medical, neurologic, and psychiatric complications related to specific illicit drugs have recently been reviewed (Sloan et al., 1998a; Brust, 2004). Although 85–90% of strokes associated with use of illicit drugs occur in the third or fourth decade, the age range reported in the literature is neonatal/perinatal to 63 years. Symptoms may occur on the background of chronic abuse, overdose, "binge" use, re-exposure after a prolonged abstinence, or even first exposure to the offending agent. Symptoms frequently occur during or within minutes to several hours (usually within 48 hours) after intravenous (IV), intranasal (IN), inhalational (IH), oral (P0), intramuscular (IM), subcutaneous (SQ), or inadvertent intra-arterial (IA) administration of drugs. Some individuals have used drugs by multiple routes.

Accumulating data indicate that there is a strong temporal association between drug use and stroke. In the San Francisco General Hospital study (Kaku and Lowenstein, 1990), there was a relative risk of 46.5 (95% CI = 6.1–354) for drug use less than 6 hours from stroke onset and 5 (95% CI = 1.4–18.1) for drug use of unknown interval from stroke onset. In the Stroke Prevention in Young Women Study (Sloan et al., 1997), cocaine use within 24 hours was associated with an ischemic stroke risk of infinity (95% CI = 2.6–infinity). Several case series (Green et al., 1990; Levine et al., 1990; Oyesiku et al., 1993) have demonstrated strong temporal relationships for alkaloidal cocaine-associated strokes and cocaine-associated intracerebral and subarachnoid hemorrhage. The Hemorrhagic Stroke Project (Broderick et al., 2003) showed that the risk of subarachnoid hemorrhage following cocaine use within 72 hours was OR = 24.97, 95% CI = 3.95–infinity. In clinical practice, the time interval between administration of the agent(s) and onset of symptoms is frequently unknown. It is often impossible to know with certainty the nature or dosage of a drug the patient has taken because of the availability of new or "designer" drugs with different chemical structures and the fact that the patient, family members, and friends are typically unreliable or naïve historians (Magder et al., 2000). It may also be difficult to determine the likelihood of a specific stroke subtype occurring with a specific drug form due to polysubstance abuse and uncertain composition of the substance abused (some other drug, adulterants).

Presenting neurologic symptoms include focal neurologic deficits, seizures, vascular headaches, depressed level of consciousness, or coma (Sloan et al., 1998a; Brust, 2004; Williams, 2004). Patients might be hypertensive or normotensive or have cardiac arrhythmias when first seen. Drug use, especially cocaine use, has been commonly associated with a history of migraine headaches without aura, headache with migrainous features, severe vascular headaches without neurologic complications immediately after drug ingestion, frequent headaches of increasing severity during "binge" use, and increasingly severe headaches with acute drug withdrawal. However, detailed assessment of migraine precipitants in drug abusers is lacking (Dhopesh et al., 1991; Dhuna et al., 1991; El-Mallakh et al., 1991). The nature and significance of the association between drug use, vascular or

migraine headaches, and stroke require further study. Most drugs have been associated with more than one stroke subtype. Some drugs are preferentially related to certain stroke subtypes. For example, heroin is most often associated with cerebral ischemia; it has rarely been linked to subarachnoid hemorrhage or intracerebral hemorrhage not due to infective endocarditis, renal or liver disease. Cocaine use by various routes is strongly associated with both ischemic and hemorrhagic stroke.

41.5. Stroke subtypes—general aspects

The relationship between stroke subtype and specific drugs has recently been reviewed (Sloan et al., 1998a; Brust, 2004; Williams, 2004). One study (Levine et al., 1991) compared the stroke subtypes in 46 patients who used alkaloidal cocaine with 63 patients who used cocaine hydrochloride, reporting from four institutions and the available medical literature, excluding patients in whom the form of cocaine taken was uncertain or mixed. Ischemic and hemorrhagic strokes were equally likely after alkaloidal cocaine use, with some cases of crack cocaine-associated ischemic stroke preceded by transient ischemic attacks. On the other hand, cocaine hydrochloride appeared more likely (about 80%) to cause hemorrhagic stroke, with approximately half of the cases occurring from ruptured cerebral saccular aneurysms or arteriovenous malformations. Cerebral infarction was significantly more common among alkaloidal cocaine users than in all cocaine hydrochloride users ($p < 0.01$). The reported relation between stroke subtype and form of cocaine used is subject to the selection bias inherent in analyzing only published cases and exclusion of a large number of other cocaine-associated stroke cases in the literature.

Various amphetamines are more likely to be associated with intracerebral hemorrhage than subarachnoid hemorrhage or ischemic stroke. Only one case of intracerebral hemorrhage associated with an arteriovenous malformation has been reported. Phenylpropanolamine is strongly associated with intracerebral hemorrhage, also unrelated to structural vascular lesions. The reasons for the differences between cocaine and amphetamine/amphetamine-like substance-associated intracerebral hemorrhages are unknown (Caplan, 1994).

41.6. Mechanisms of ischemic stroke

The mechanisms of brain ischemia associated with illicit drug use or abuse have been extensively reviewed (Sloan et al., 1998a; Brust, 2004; Williams, 2004). Selected case reports and case series have added to the heterogeneity of mechanisms by which drugs might cause ischemic stroke. The mechanisms by which drugs (including ethanol) might produce stroke are summarized in Table 41.4. These mechanisms may be novel or complex. In fact, the mechanism(s) in a susceptible individual may be multifactorial or indirect, consisting of multiple effects of a single agent (cocaine-vasoconstriction, various hemostatic effects), drug interaction (cocaine, ethanol), indirect effects by induction of embolic or arrhythmogenic cardiac disease, or an interaction between drug use, preexisting cardiovascular or cerebrovascular disease, or stroke risk factors.

41.6.1. Arterial vasoconstriction

Transient or chronic arterial vasoconstriction has frequently been suspected as being a mechanism for ischemic stroke following drug use. Neuroimaging evaluation of acute and chronic cocaine users with single-photon emission computed tomography (SPECT), positron emission tomography (PET) and transcranial Doppler (TCD) (as reviewed by Sloan et al., 1998a) suggest that cocaine and the cocaine metabolite benzoylecgonine may cause transient or prolonged cerebral vasoconstriction. TCD monitoring of the effects of acute cocaine administration reveals increased pulsatility index, suggesting an increased cerebrovascular resistance via distal vasoconstriction in the middle cerebral artery (Fayad et al., 1992). SPECT studies may show patchy areas of hypoperfusion despite a normal brain MRI scan, with or without accompanying cognitive deficits. The pattern of reduced cerebral blood flow may be in a scalloped pattern in the cortical pial artery distribution (Mena et al., 1990), even in a multifocal, bilateral frontal, and temporal distribution (Tumeh et al., 1990) following acute or chronic cocaine intoxication in humans. In one case, a 33-year-old woman had a small left lateral superior parietal convexity infarction within 24 hours after she snorted cocaine. Angiography revealed slow flow and middle cerebral artery branch occlusion (Sloan et al., 1991). Post mortem examination may show infarct-related arteries being smaller than their contralateral counterparts, with normal endothelium, abnormal internal elastic lamina infolding, and tunica media degeneration (Levine et al., 1990). Whether these findings reflect vasoconstriction, reduced vessel caliber related to decreased demand for blood flow, or some other reason is not clear. As mentioned previously, large vessel intracranial and extracranial steno-occlusive disease (progressive stenosis, occlusion) has been reported following use of heroin, cocaine, amphetamines, and LSD. In patients with chronic vasculopathy/vasoconstriction,

Table 41.4

Mechanisms of cerebral ischemia associated with drug use/abuse

	Ethanol	Heroin/ opiates	Cocaine	Amphetamines	OTC sympathomimetics	Phencyclidine	LSD	Ts and blues	Marijuana	Ecstasy
Arterial vasoconstriction										
Vasospasm	+	−	+	+	+	+	+	−		
Vasculopathy	−	+	+	+	−	−	+	−		
Arteritis	−	+	+	+	−	−	+	+		
Delayed hypersensitivity/ immunologic	−	+	−	−	−	−	−	−		
Foreign body embolization	−	+	−	+	−	−	−	+		
Structural heart disease										
Arrhythmias	+	−	+	+	−	+	−	−		
Cardiomyopathy	+	+	+	+	−	−	−	−		
Myocardial infarction	−	−	+	−	−	−	−	−		
Endocarditis	−	+	+	+	−	−	−	−		
Small vessel disease	−	+	+	−	−	−	−	−		
Prothrombic tendencies										
Reduced fibrinolysis	−	−	+	−	−	−	−	−		
Platelet activation/aggregation	+	−	+	−	−	−	−	−		
Anticardiolipin antibodies	−	−	+	−	−	−	−	−		
In situ thrombosis	−	−	+	−	−	−	−	−		
Meningovascular syphilis	−	−	+	−	−	−	−	−		
Unknown									+	+

+, known association; −, no known association; OTC, over-the-counter; LSD, lysergic acid diethylamide; Ts and Blues, tripelennamine and pentazocine.
From Sloan et al. 1998a.

segmental or multifocal narrowing of the vessel might be due to either a primary toxic effect or perhaps a complication of unrecognized subarachnoid hemorrhage. More pathologic data are needed to clarify the nature of the large-vessel vasculopathy that occurs in drug users.

41.6.2. Arteritis

A number of illicit drugs have been associated with angiographic findings consistent with "arteritis" in any of several vascular territories (as reviewed by Sloan et al., 1998a). These include heroin, amphetamines, LSD, and Ts and Blues. In a number of cases, patients abused multiple illicit drugs. In some cases, disordered immunity may play a role. For example, heroin addicts have been shown to manifest a variety of immunologic aberrations. The occurrence of stroke long after drug administration or upon re-exposure after a prolonged abstinence suggests that delayed hypersensitivity reactions may be the proximate cause of some cerebral ischemic events. However, pathologic data are limited.

A classic study (Citron et al., 1970) reported vascular lesions in 14 polysubstance abusers. Acutely, there was fibrinoid necrosis of the media and intima with infiltration by neutrophils, eosinophils, lymphocytes, and histiocytes; later, there was destruction of muscular and elastic components, replacement by collagen, and often a nodular ("nodose") bulge with nearly aneurysmal dilatation. Since only the muscular arteries and arterioles were affected, these changes were believed to be consistent with peri-arteritis nodosa despite the absence of Australia antigen. Biopsy studies in cocaine abusers have revealed vasculitis involving small cortical vessels and multinucleated giant cells (Krendel et al., 1990) or lymphocytic infiltration in perivascular collections and within the walls of arterioles, endothelial swelling of small arterioles, and scattered foci of interstitial edema (Fredericks et al., 1991). It is thus probable that lone cocaine use may induce a non-necrotizing, non-leukocytoclastic small-vessel arteritis (Fredericks et al., 1991).

41.6.3. Small-vessel disease

Subcortical and lacunar infarcts have been reported in association with cocaine and heroin use, at times associated with hypertension and smoking. When performed, cerebral angiography has usually been normal, but patients with middle cerebral artery stenosis (Daras et al., 1991) and distal middle cerebral artery or bilateral anterior cerebral artery occlusions (Peterson et al., 1991) have been reported. Possible explanations for these infarcts include vasospasm of small penetrating arteries, vasospasm of main-stem cerebral arteries with ischemia in the distribution of the penetrating arteries, vasospasm superimposed on macroatheroma or microatheroma, embolism, or some other mechanism.

41.6.4. Structural heart disease

Illicit drug use may induce a variety of cardiac abnormalities that may predispose to cerebral embolism. Infective endocarditis, with septic embolization to the brain, has long been known to be a cause of stroke in the intravenous drug user (Salgado et al., 1989; Hart et al., 1990). Two interesting cases have shown fatal stroke related to distal aortic occlusion due to *Aspergillus flavus* endocarditis despite amphotericin B therapy (Light et al., 1991) and right occipital lobe and internal capsule infarction associated with an extracardiac shunt due to a right middle lobe peripheral arteriovenous fistula (Stagaman et al., 1990).

Myocardial injury can also occur following long-term heroin or amphetamine use (Lam et al., 1988; Sloan and Mattioni, 1992). Cocaine-associated cardiomyopathy can be reversible or chronic (Kloner et al., 1992). Significant wall motion abnormalities also occur, thus predisposing toward left ventricular apical thrombi (Petty et al., 1990; Sauer, 1991) and cardiogenic embolism. In patients who die from cocaine intoxication, the presence of contraction bands or cardiomyopathy may add to the cocaine user's susceptibility to supraventricular and ventricular arrhythmias (Isner and Chokshi, 1991; Kloner et al., 1992). Patients with underlying structural heart disease who continue to abuse drugs are at risk for myocardial infarction, life-threatening cardiac arrhythmias, and major cerebrovascular events. Two cases of embolic stroke illustrate that one mechanism by which cocaine and phencyclidine can cause stroke is by triggering expression of a known cardiac source of cerebral embolism, atrial fibrillation, or acute myocardial infarction, due to cardiac stimulation or platelet effects (Sloan et al., 1991; Sloan and Mattioni, 1992). The incidence of this phenomenon is unknown.

41.6.5. Foreign body embolization

Embolization of talc, corn starch, and other particles to the brain have been reported in abusers of heroin, meperidine, paregoric, methylphenidate, and Ts and Blues. Embolic particles have been demonstrated in the central nervous system, medial medullary vessels, retina, lungs, liver, and spleen. Such microemboli may reach the brain, especially if pulmonary emboli result in pulmonary hypertension and the opening of extracardiac shunts (Sloan et al., 1998a; Brust, 2004).

41.6.6. Prothrombotic tendencies

Limited clinical data exist to explore the relationship between drug use, changes in hemostasis, and cerebrovascular events. Three cases (Levine et al., 1990; Konzen et al., 1995) of crack cocaine-associated stroke have been reported in which an intraluminal filling defect consistent with in situ thrombus was angiographically shown in the extracranial internal carotid artery. A carotid thrombectomy in one case showed a white fibrin clot obstructing the vessel. In another case, angiography showed a thrombus in the proximal right internal carotid artery with associated right middle cerebral artery occlusion. Follow-up carotid duplex study 8 days later showed a 15% right internal carotid artery stenosis but no clot (Konzen et al., 1995). Unfortunately, detailed evaluation of hemostasis was not performed. However, these observations suggest that cocaine-related thrombus formation may be transient or lead to artery-to-artery embolization and stroke. Whether in situ thrombosis occurs in the intracranial circulation, with or without accompanying vasospasm, is speculative.

41.7. Mechanisms of intracranial hemorrhage

The mechanisms of brain hemorrhage associated with drug use or abuse have been extensively reviewed (Green et al., 1990; Levine et al., 1991; Sloan, 1993; Caplan, 1994; Brust, 2004). Recent case reports and case series (as reviewed by Sloan et al., 1998a) have added to the heterogeneity and complexity of mechanisms by which drugs may cause hemorrhagic stroke. The mechanisms by which drugs (including ethanol) may produce hemorrhagic stroke are summarized in Table 41.5. The association between drug-induced intracranial hemorrhage and induction of microaneurysms and lesions that affect arterioles, capillaries, and venules has already been discussed. As with cerebral ischemia, the mechanisms may be novel in some cases.

41.7.1. Hypertension

Use or abuse of drugs may lead to acute, transient, or persistent severe hypertension. It has been proposed (Caplan, 1988) that hypertension might lead to intracerebral hemorrhage by three mechanisms: (1) damage to cerebral arterioles, which eventually rupture; (2) acute hypertension of sufficient degree to overcome autoregulation and lead to "breakthrough perfusion"; or (3) reperfusion of ischemic brain tissue. Experimental work in rats (Burke et al., 1987) suggests that acute hypertension may cause hyperperfusion in the cerebellum, parietal gray matter, thalamus, striatum, and pons. Several investigators (Shibata et al., 1991; Caplan, 1994; Kokkinos and Levine, 1994; Brust, 2004) recently reviewed intracerebral hemorrhage attributable to drugs and found that hypertension was frequently noted, at times to extreme levels, in patients examined soon after onset of hemorrhage related to amphetamines and cocaine and, to a lesser extent, other sympathomimetics. The hemorrhage location, if specified, was lobar in 10 of 14 (71%) amphetamine-related cases, 12 of 19 (63%) PPA-related cases, and 26 of 45 (57%) cocaine-related cases, whether or not an underlying lesion was present. This pattern is atypical for hypertensive intracerebral hemorrhage (Green et al., 1990; Levine et al., 1991) and suggests that other mechanisms may be operant in these cases. In fact, it is often difficult to know how often acute hypertension plays a role since patients may be normotensive when first seen. However, in the Baltimore–Washington Cooperative Young Stroke Study (Sloan et al., 1996), 58.3% of patients with cocaine and hypertension had intracerebral hemorrhage in typical hypertensive sites. In heroin and cocaine users, development of nephropathy with malignant hypertension may be associated with intracerebral hemorrhage (Kibayashi et al., 1995; Brust, 2004). Severe or malignant hypertension due to phencyclidine has also resulted in intracranial hemorrhage. With PPA, the role of hypertension in the production of symptoms is controversial.

41.7.2. Unmasking pre-existing lesions

In recent reviews of hemorrhagic stroke attributable to illicit drugs (Green et al., 1990; Levine et al., 1991; Caplan, 1994; Kokkinos and Levine, 1994; Brust, 2004), parenchymatous intracerebral hemorrhage due to cocaine was associated with an underlying vascular lesion in 16 of 35 patients (46%), with 12 arteriovenous malformations (10 with lobar hemorrhages), 3 aneurysms, and 1 glioma. Only one patient with amphetamine-related intracerebral hemorrhage had an arteriovenous malformation and no PPA patient had a demonstrable structural vascular lesion.

Of 48 reviewed patients with cocaine-associated subarachnoid hemorrhage (Oyesiku et al., 1993), 39 (81%) had saccular aneurysms on cerebral angiography or autopsy. For other patients with documented drug-associated subarachnoid hemorrhage, one PCP case was related to a saccular aneurysm (Sloan et al., 1991), one PCP case was associated with perforation of the basilar artery where embryologic development and regression of the trigeminal artery occurred (Boyko et al., 1987), one heroin case was related to

Table 41.5

Mechanisms of intracranial hemorrhage associated with drug use/abuse

	Type of drug						
Mechanism	Ethanol	Heroin/opiates	Cocaine	Amphetamine	OTC sympathomimetics	Phencyclidine	Ts and blues
Hypertension	+	+	+	+	+	+	+
Unmasking preexisting lesions							
Aneurysm	+	−	+	−	−	+	−
Arteriovenous malformation	+	+	+	+			−
Tumor	−	−	+	−	−	−	−
Lesion induction							
Microaneurysms	−	−	+	+	−	−	−
Arterioles	−	−	+	+	−	−	−
Venules	−	−	+	+	−	−	−
Other						+	−
Arteritis/vasculopathy		+	+	+	+		+
Endocarditis	−	+	+	+	−	−	−
Immune perturbations	−	+	−	−	+	−	−
Hemostatic effects							
Increased fibrinolysis	+	−	−	−	−	−	−
Decreased clotting factors	+	+	−	−	−	−	−
DIC	+	−	−	−	−	−	−
Thrombocytopenia/prolonged bleeding time	+	+	+	−	−	−	−
Drug interactions							
MAO inhibitors	−	−	−	+	+	−	−
NSAIDs	−	−	−	−	+	−	−
Heparin	−	+	−	−	−	−	−
OTC sympathomimetics	−	−	−	−	+	−	−
Ethanol	+	+	+	+	−	+	−
β-Blockers	−	−			+	−	−
Reperfusion	+		+		−	−	−
Combination	+	+	+	+	+	+	−

+, known association; −, no known association; DIC, disseminated intravascular coagulation; MAO, monoamine oxidase; OTC, over-the-counter; NSAIDs, nonsteroidal antinflammatory drugs.
From Sloan et al. 1998a.

an arteriovenous malformation (Sloan et al., 1991), and one amphetamine case was associated with irregular arterial beading and luminal irregularity and 2-mm fusiform aneurysmal dilation of an anterior temporal branch of the middle cerebral artery (Matick et al., 1983). Three recent studies (Nanda et al., 2000; Conway and Tamargo, 2001; Howington et al., 2003) have examined the relationship between cocaine use, aneurysm rupture and vasospasm after spontaneous subarachnoid hemorrhage. Compared with controls, cocaine users are younger, and are more likely to have smaller or anterior circulation aneurysms (Nanda et al., 2000; Conway and Tamargo, 2001). It is believed that acute hypertension is the likely precursive factor in cocaine-induced aneurysm rupture (Oyesiku et al., 1993). In addition, cocaine users have a 2.8-fold increased risk of developing angiographic vasospasm (Howington et al., 2003) and 3.9-fold increased risk of developing clinical vasospasm compared with controls.

41.7.3. Arteritis/vasculopathy

Angiographic findings consistent with large-vessel arteritis or vasculitis has been reported in patients with intracerebral hemorrhage who abuse amphetamines, heroin, Ts and Blues, PPA, EPH, PSE, and diethylpropion hydrochloride (as reviewed by Caplan, 1994; Sloan et al., 1998a; Brust, 2004; Williams, 2004). Pathological changes have included medial necrosis without inflammation following intravenous methamphetamine (Shibata et al., 1991); necrotizing vasculitis of small arteries and veins, particularly prominent in the intima, with infiltration of polymorphonuclear leukocytes and subsequent thickening and reduction of the lumen, areas of vessel occlusion, and fragmentation of the elastic lamina, subarachnoid hemorrhage, fibroblastic proliferation, and recent small gray matter infarcts (Glick et al., 1987); and small-vessel vasculitis affecting arterioles and venules (Tapia et al., 1993). It is therefore possible that the multiple intracerebral hemorrhage patient of Green et al. (1990) reflects rupture of multiple arterioles or venules induced by cocaine. However, three autopsy studies (Kibayashi et al., 1995; Aggarwal et al., 1996; Nolte et al., 1996) reviewed selected brain samples from 50 autopsy cases of cocaine-related cerebrovascular disease failed to reveal evidence of vasculitis. In one study (Aggarwal et al., 1996) of 12 patients with intracerebral or subarachnoid hemorrhage, intracranial arterioles revealed slight brainstem intravascular hyalinization in one and minimal cortical vessel intimal fibrin formation in another; occasional polymorphonuclear leukocytes were noted in the lumina of pontine perforating arterioles in two others. Since vasculitis is difficult to demonstrate, it thus appears likely that cocaine may induce a vasculopathy by direct or immunologic mechanisms, and acute transient hypertension (in some cases) promotes rupture of damaged vessels resulting in hemorrhage (Caplan, 1988).

41.7.4. Infective endocarditis

Drug users who develop endocarditis are younger, have less underlying structural heart disease, more commonly have *S. aureus* as the offending pathogen, and more often have primary hemorrhagic stroke than non-drug users (Hart et al., 1987; Salgado et al., 1989; Hart et al., 1990). Brain hemorrhage tends to occur at the time of presentation and is associated with uncontrolled *S. aureus* infection. Hemorrhages are often lobar and may be single or multiple. Common mechanisms of brain hemorrhage include septic arteritis and hemorrhagic transformation of ischemic stroke due to septic embolism. Hemorrhagic transformations may be asymptomatic or confluent, with hematoma formation and worsening. Rupture of mycotic aneurysms is rare.

41.7.5. Reperfusion

The contribution of reperfusion of ischemic brain to the production of brain hemorrhage following isolated use has recently been suggested (Caplan, 1988; Levine et al., 1990, 1991). Several cases of hemorrhagic transformation of ischemic cerebral infarction have been reported (Levine et al., 1990; Sauer, 1990; Daras et al., 1991; Konzen et al., 1995). These hemorrhagic infarctions might also be the result of the natural history of the underlying stroke mechanism (Sauer, 1990). Whether parenchymatous or confluent hemorrhagic infarctions might be produced by drug use is presently unknown.

41.7.6. Drug interactions

The role of drug interactions, either additive or synergistic, in the production of brain hemorrhage following drug use has been observed with ethanol, monoamine oxidase inhibitors, beta-blockers (nadolol), nonsteroidal anti-inflammatory drugs (NSAIDs, such as indomethacin), caffeine, EPH, PSE, and heparin may interact with ingested OTC sympathomimetic drugs or illicit drugs with adverse consequences (as reviewed by Sloan et al., 1998a). For example, approximately half of the cases reported in association with PPA use have occurred in combination with one or more other pharmacologic agents (e.g., alcohol, caffeine, PSE,

EPH, and monoamine oxidase inhibitors). In some instances, hypertensive crisis and multiple or sequential intracerebral hematomas have been reported (Kase et al., 1987; Levine et al., 1990; Sloan et al., 1998a). As with ischemic stroke, cocaine-associated intracerebral hemorrhage might be associated with ethanol use (Green et al., 1990; Levine et al., 1990; Sloan et al., 1991). A patient who had an aneurysmal subarachnoid hemorrhage following combined PCP and ethanol use has also been reported (Sloan et al., 1991). Possible mechanisms in these cases include additive–synergistic effects on blood pressure leading to hemorrhage (Caplan, 1988), at times with the unmasking of preexisting cerebral macro- or microvascular lesions (Rumbaugh et al., 1971, 1976; Nalls et al., 1989), or ethanol-induced reduction in hepatic metabolism with resultant prolongation of drug effects (Hoyumpa, 1984). The frequency of adverse drug interactions in patients with drug-associated stroke is unknown.

41.8. Diagnosis, management, and outcome

41.8.1. Diagnosis

When confronted with a stroke patient, particularly one who is less than 50 years old and without stroke risk factors, the clinician should have a high index of suspicion for drug use or abuse. This is especially true in large metropolitan and inner city regions. It is well known that the history may be unreliable. In fact, one study of cocaine use in an inner city walk-in clinic (McNagny et al., 1992) showed that 72% of men with positive urine toxicology screens denied illicit drug use in the 3 days before sampling. However, such patients were more likely to admit to "any illegal drug use" (87.5%) than to the more specific "any form of cocaine" use (60.6%) within the prior year ($p < 0.0001$). Therefore, one should repeatedly (if necessary) question the patient, family members, and friends for a history of drug use by all possible routes. One should look for associated physical stigmata of drug use, such as hypertension, cardiac arrhythmias, needle marks, other cutaneous signs, other organ system signs (nephropathy), signs of endocarditis, and so forth (Sloan et al., 1998a; Brust, 2004).

All such patients should be evaluated with toxicologic screens of urine, blood, pill vials, and even gastric juice. A variety of methods are available: thin-layer chromatography (TLC), gas–liquid chromatography (GOLC), high-pressure liquid chromatography (HPLC), combined gas chromatography–mass spectroscopy (GC–MS), radioimmunoassay (RIA), and enzyme-multiplied immunoassay (EMIT). All tests are highly sensitive, with GC–MS and GC–TLC being highly specific. Confirmatory testing, typically using a second method, is recommended to minimize the chance of false positives. The duration of detectability is generally about four urinary half-lives, typically up to 2–3 days, except for severe PCP poisoning (2–4 weeks) or marijuana metabolite (1 month). It may be lengthened by significant kidney, liver, or heart disease; manipulation of urinary pH; or pattern of drug use (as reviewed by Sloan et al., 1998a). For example, chronic users of high doses of cocaine may excrete benzoylecgonine for 10–22 days (Weiss et al., 1988; Burke et al., 1990).

For ischemic stroke patients, an appropriate neurodiagnostic evaluation, including CT scan, MRI scan, selected cardiologic investigations (cardiac enzymes; electrocardiogram; echocardiography, including contrast and transesophageal; and Holtor monitoring) and non-invasive vascular tests (carotid, transcranial Doppler) and cerebral angiography should be performed to determine the stroke mechanism. Cerebral angiography in young adult stroke patients, in general, has a high yield, particularly if performed early after stroke onset (Smoker et al., 1987). In patients with drug abuse, it may reveal extracranial or intracranial large-vessel lesions, such as stenosis, occlusion, or findings consistent with arteritis. The role of magnetic resonance angiography and computed tomographic angiography in this setting has not been established. Extensive hematologic testing can be considered in cocaine-related stroke (Isner and Chokshi, 1991; Sloan et al., 1998a).

For patients with intracerebral hemorrhage (especially lobar) and subarachnoid hemorrhage, cerebral angiography has a high yield for a saccular aneurysm or arteriovenous malformation, especially in cocaine users (Caplan, 1994; Kokkinos and Levine, 1994) and those with sympathomimetic abuse (Williams, 2004). In the appropriate setting, brain or leptomeningeal biopsy, or both, can be pursued to make the diagnosis of vasculitis. For intravenous drug users, human immunodeficiency virus (HIV) testing is strongly recommended.

41.8.2. Management

Once a stroke is recognized as drug-related, acute intervention before diagnosis of a specific mechanism may require specific pharmacologic treatment of hypertension; urinary acidification (PCP), urinary alkalinization (amphetamines), and gastric lavage (PCP) to enhance drug elimination; delineation and treatment of the cause of fever; and, in some cases, management of increased intracranial pressure. Patients with ischemic stroke may be considered for intravenous thrombolytic therapy; however, data are scant on the safety of thrombolysis

in this setting and its use should be carefully considered (Williams, 2004). All ischemic stroke patients should be treated with appropriate secondary preventative antithrombotic therapy with anticoagulants reserved for clear indications and demonstration of abstention from drug use. Patients with intracerebral hematomas and subarachnoid hemorrhage can additionally be treated with empiric or standard medical and surgical therapy, as appropriate. Underlying structural lesions, such as aneurysms and arteriovenous malformations, can be treated with surgical or interventional neuroradiologic techniques, or both, as appropriate. Although unproved, patients with arteritis may benefit from drug discontinuation, empiric high-dose steroids followed by gradual taper, and interval angiography to document resolution (Sloan et al., 1998a). Patients with true vasculitis (e.g., periarteritis nodosa, "central nervous system vasculitis") should be treated with high-dose steroids and cyclophosphamide (Kokkinos and Levine, 1994). Of course, all patients who survive the ictus should ideally be referred to drug-treatment programs.

41.8.3. Outcome

The short- and long-term outcome in large series of patients with drug-associated stroke has infrequently been reported. In a study by Kaku and Lowenstein (1990), mortality was somewhat higher in the 47 patients whose strokes were strongly linked to drug abuse (occurrence <6 hours after drug use) than among the non-drug users ($p = 0.10$). In a study by Sloan et al. (1991), 11 patients were followed from 1 to 14 months: 3 made complete recoveries, 2 had mild residual, 1 had moderate residual, 1 died from a pulmonary embolism 1 month after intracerebral hemorrhage, 2 could not be located, and 2 refused to be followed. Peterson et al. (1991) reported the outcome in 16 of 19 patients with cocaine-associated cerebral infarctions: 1 died in a nursing home, 5 received in-patient treatment for depression, 7 were discharged home, and 3 left the hospital against medical advice. Daras et al. (1991) reported the outcome of 18 patients with cocaine-associated cerebral infarctions: 2 recovered completely, 2 died from aspiration pneumonia, and 14 were left with moderate to severe neurologic deficits. In the Baltimore–Washington Cooperative Young Stroke Study (Sloan et al., 1998b), there was no difference in mortality between drug users (13.7%) and non-drug users (10%), although drug users were somewhat more likely to be transferred to a rehabilitation facility (24% versus 17%) and somewhat less likely to go home or to a self-care environment (58% versus 70%).

Peterson et al. (1991) reported the outcome of 15 patients with intracerebral hemorrhage: 5 died in the hospital, 1 was discharged to a nursing home, 3 were transferred to a rehabilitation facility, and 6 were discharged home after prolonged hospitalization. Of the well-documented intracerebral hemorrhages attributable to cocaine, amphetamines, and phenylpropanolamine, the mortality has been approximately 25–35% (Caplan, 1994; Kokkinos and Levine, 1994; Brust, 2004), with significant morbidity in survivors. In the Baltimore–Washington Cooperative Young Stroke Study (Sloan et al., 1996), there was a trend ($p = 0.094$) towards a higher mortality rate in intracerebral hemorrhage patients with any drug use.

Simpson et al. (1990, 1991) reported 150 consecutive patients with subarachnoid hemorrhage and found that the distribution of severe disability or vegetative status or death was significantly higher among the 17 patients (16 aneurysmal, 1 arteriovenous malformation) with intravenous drug abuse than among the 133 patients with no history of drug abuse. Oyesiku et al. (1993) reviewed cases of cocaine-associated subarachnoid hemorrhage and found a mortality of atleast 23 of 48 patients (48%). In two studies of 575 subarachnoid hemorrhage patients (Nanda et al., 2000; Conway and Tamargo, 2001), there was no difference in discharge Glasgow Outcome Scale score between cocaine users and non-users. However, a more recent study of 108 subarachnoid hemorrhage patients (Howington et al., 2003) revealed that cocaine use was associated with a 3.3-fold greater risk of a poor outcome (Glasgow Outcome Scale score 1–3). The reasons for these discrepant results are unclear.

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Chapter 42

Stroke, migraine, and headache

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42.1. Introduction

The relationship between migraine and ischemic stroke is complex and simply can be described as bidirectional. Stroke can cause headache and migraine; and migraine is now considered as an independent stroke risk factor for ischemic stroke, especially in a certain subpopulation of patients (Tzourio et al., 2000; Bousser and Welch, 2005; Tietjen, 2005; Lampl and Marecek, 2006). Headache is reported in 17–34% of the cases of ischemic stroke. It is more frequent in posterior circulation (basilar territory) strokes than anterior circulation (carotid territory) ischemia and rarely occurs in lacunar strokes (Olesen et al., 1993; Jorgensen et al., 1994; Tentschert et al., 2005; Mitsias et al., 2006). Conversely stroke is more common in patients with migraine and unspecified headache. It is this relationship between stroke and migraine or unspecified headache that is the subject of discussion in this chapter. Both stroke and migraine are common conditions and their symptoms overlap. Thus one condition may mimic the other one, and make it hard to clearly differentiate between them. The estimated incidence of new or recurrent strokes is more than 700,000 per year in the USA, of which 500,000 are new strokes and 200,000 recurrent strokes (Thom et al., 2006). Of these, 85% are ischemic and 15% are hemorrhagic strokes. The most common risk factors for stroke include age, hypertension, dyslipidemia, smoking, diabetes mellitus, and cardiovascular diseases. Other less common risk factors include coagulation abnormalities, obesity, heavy alcohol intake, family history, and migraine headaches. Several studies have clearly shown that migraine with aura is an independent risk factor for ischemic stroke in women under the age of 45. The results for elderly men and women are inconsistent (Tzourio et al., 2000; Bousser and Welch, 2005; Tietjen, 2005; Lampl and Marecek, 2006).

International Headache Society (IHS) guidelines published in 1988 and revised in 2004 (Headache Classification Committee of the International Headache Society, 1988, 2004) describe four categories of primary headaches: (1) migraine, (2) tension-type headache, (3) cluster headache and other trigeminal autonomic cephalgias, and (4) other primary headaches. Migraine is a chronic condition characterized by recurrent, unilateral, usually pulsatile headaches, typically lasting 4–72 hours and associated with nausea, vomiting, photophobia and phonophobia. Migraine is two to three times more common in women than in men and it is estimated that approximately 18% of women and 6% of men in the USA suffer from it. The peak prevalence is during midlife in both men and women and approximately 28 million people in the USA have migraine attacks each year (Stewart et al., 1992; Lipton et al., 2001). According to International Headache Society (IHS) guidelines, migraine can be classified as migraine with aura (classic migraine) and migraine without aura (common migraine). Migraine with aura accounts for about one-third of the migraine patients, whereas the rest are migraine without aura. The aura can take the form of visual disturbances, speech changes, paresthesias, weakness, vertigo, dizziness, and tinnitus. The typical aura symptoms develop over 5–20 minutes and last less than 60 minutes. If the aura lasts more than 60 minutes, it is defined as a prolonged aura. Under the revised IHS classification (2nd edition, 2004) the term "complicated migraine" has been excluded and different types of complications of migraine are described separately as individual entities, like chronic migraine, status

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migrainosus, persistent aura without infarction, migrainous infarction, migraine triggered seizure, and so on. Migrainous infarction is considered a complication of migraine with aura and is defined as: (1) if the aura symptoms are typical of previous migraine attacks, (2) one or more aura symptoms lasts longer than 60 minutes, (3) neuroimaging shows an infarction in the appropriate relevant territory, and (4) all other causes are excluded. Other migraine variants include retinal migraine, abdominal migraine, basilar-type migraine, typical aura without headache and familial hemiplegic migraine. Ophthalmoplegic migraine is now categorized as cranial neuralgia.

42.2. Migrainous infarction versus migraine-related stroke

Recently there had been a suggestion to redefine migrainous stroke (migrainous cerebral infarction, migraine-induced stroke) as originally classified in the IHS classification (1st edition). The 1988 IHS classification described migrainous infarction as "complicated migraine," in which the neurological deficit was in the same vascular distribution as migraine with aura, the symptoms were not completely reversible in one week, and the neuroimaging studies confirmed the stroke, provided all other known causes of stroke were excluded. However, there have been several studies in which migrainous infarction was reported in patients suffering from migraine without aura, raising a question that the term migrainous infarction should not be restricted to the patients who suffer from migraine with aura (Welch and Levine, 1990; Rothrock et al., 1993; Narbone et al., 1996; Ebinger et al., 1999). Welch and Levine (Ebinger et al., 1999) proposed an extended classification of "migraine-related stroke" to include migraine without aura and migrainous infarction. Other authors (Dayno and Silberstein, 1997) have suggested that the diagnosis of migraine-induced stroke should be reserved only for those patients in whom no other stroke risk factor can be identified and the rest should be classified as migraine-related strokes. Because of this ambiguity the incidence of migrainous infarction has been reported as anywhere between 1% and 40% of migraine-associated strokes, according to various studies. For example, the European Multicenter WHO Collaborative Study (Chang et al., 1999) showed that 20–40% of strokes in migrainous women are migraine-induced strokes (migrainous strokes). Henrich et al. (1986) in their Oxfordshire Community Stroke Project reported the occurrence of migrainous stroke at a rate of 3.36/100,000 per annum, whereas in the Dijon Stroke Registry (Sochurkova et al., 1999) the incidence was 0.8/100,000 per annum. Arboix et al. (2003) in their Sagrat Cor Hospital of Barcelona stroke registry study (fulfilling the strict 1988 IHS criteria), showed that the incidence of migraine-induced stroke was 13.7% of infarcts in young adults and 0.8% of all ischemic strokes. Similar results (i.e. 0.8% of all acute strokes) were reported by Linetsky et al., (2001).

The revised IHS classification of 2004 (Headache Classification Committee of the International Headache Society, 2004), as mentioned above, has removed the term "complicated migraine" and modified the definition of migrainous infarction but does not fully address the issue of migraine-related stroke or migrainous infarction in the context of migraine without aura. In their comments the authors suggest that "ischemic stroke in a migraine sufferer may be categorized as cerebral infarction of other cause coexisting with migraine, cerebral infarction of other cause presenting with symptoms resembling migraine with aura, or cerebral infarction occurring during the course of a typical migraine with aura attack," probably implying the first two categories as migraine-related stroke, because the term migrainous infarction is reserved for the last category. The prognosis for these patients is reported to be quite favorable with good functional outcome (Hoekstra-van Dalen et al., 1996; Arboix et al., 2003).

42.3. Epidemiology/prevalence

The initial study to suggest the association between migraine and ischemic stroke was the Collaborative Group for the Study of Stroke in Young Women published in 1975 (Collaborative Group for the Study of Stroke in Young Women, 1975), which showed that migraine was present in 34% of the ischemic stroke cases and in only 24% of the neighborhood controls (odds ratio [OR] = 1.7). The data on the prevalence of a migraine history in stroke patients has been variable. A French study showed that migraine was present in 60% of ischemic stroke patients as opposed to 30% of the controls (Tzourio et al., 1995). In the European WHO Collaborative Study, migraine prevalence was reported to be 25% compared to the 13% of the controls (Chang et al., 1999). Conversely the estimated risk of ischemic stroke in women with migraine was reported as 19 per 100,000 women per year in the French study (Tzourio et al., 1995), while Henrich and Horwitz (1989) reported that the annual incidence rate of migrainous cerebral infarction among adult migraine population was 3.36/100,000.

Recently Etminan and others in their meta-analysis of 11 case-control and 3 cohort studies showed that the relative risk of ischemic stroke among patients with any type of migraine was 2.16 (95% CI = 1.89–2.48) and increased to eight fold (relative risk 8.72 with 95%

CI = 5.05–15.05) in those patients who were on oral contraceptives (Etminan et al., 2005).

42.4. Risk of ischemic stroke with migraine

As mentioned above, to date there have been several studies that have clearly demonstrated the association between migraine and ischemic stroke. Migraine is well established as an independent stroke risk factor in women under the age of 45 and who suffer from migraine with aura. This risk is further increased in women who use oral contraceptives, smoke, and have a history of hypertension. A brief overview of these studies is presented below.

In a French case control study of women under the age of 45 who were hospitalized for ischemic stroke, 60% (95% CI = 48–71%) of the cases had migraine compared to 30% (95% CI = 23–37%) of the controls (Tzourio et al., 1995). This risk persisted even after controlling for age, hypertension, smoking, and use of oral contraception. Women with migraine had more than a three-fold increased stroke risk compared to women without migraine. The odds ratio (OR) for women having migraine with aura was 6.2 (95% CI = 2.1–18.0) and for those without aura was 3.0 (95% CI = 1.5–5.8). The risk was further increased in those who also smoked (OR 10.2) or were on oral contraceptives (OR 13.9).

The Physician's Health study, a prospective study of approximately 22,000 male physicians between 40 and 84 years of age, showed that the relative risk for ischemic stroke was 2.0 (95% CI = 1.10–3.64) in migraine patients (Buring et al., 1995). This study did not contain information about the type of migraine.

The European Multicenter WHO Collaborative Study (Chang et al., 1999), concluded that the risk of ischemic stroke in women of child bearing age (20–44 years) with migraine was increased more than three-fold compared to non-migraine controls (OR 3.54 with 95% CI = 1.30–9.61). Although the risk was further increased in patients who suffered from migraine with aura, it did not reach statistical significance. Family history of migraine, with or without a personal history of migraine, was independently associated with an increased odds ratio for both ischemic and hemorrhagic stroke. The study also showed that smoking, high blood pressure, and use of oral contraceptives had more than multiplicative effect on the odds ratio for ischemic stroke associated with migraine.

The Italian Research Council Study Group on Stroke in the Young, a case control study of 308 patients aged 15–44 with either transient ischemic attacks (TIA) or stroke, concluded that the attributable risk of cerebral ischemia in women below the age of 35 was 20% (Carolei et al., 1996). They calculated the absolute annual risk of stroke as 52 per 100,000 patients having migraine with aura. The study did not show any significant risk of cerebral ischemia in all men, and women above the age of 35. A German case control study also showed similar results (Schwaag et al., 2003). The odds ratio for an overall stroke risk in their migraine population, of both men and women under the age of 46, was 2.11 (95% CI = 1.16–3.82). This risk was substantially increased in people under the age of 35, with an odds ratio of 3.26 (95% CI = 1.33–7.98). This study excluded patients with migrainous infarction.

In the Women's Health study, a prospective cohort study of approximately 40,000 US health professionals, age 45 and above, the adjusted hazards ratio (HR) of ischemic stroke was 1.71 (95% CI = 1.11–2.66) in participants who reported migraine with aura (Kurth et al., 2005). This risk was further increased in those under the age of 55 (HR 2.25; 95% CI = 1.30–3.91). No such association was detected for migraine without aura. The absolute increased risk is reported as 3.8 additional cases per year per 10,000 women.

The Atherosclerosis Risk in Communities Study (Stang et al., 2005), a bi-racial cohort of 12,750 African-American and white men and women, reported that migraine with aura was strongly associated with stroke symptoms (OR 5.46; 95% CI = 3.64–8.18), TIA symptoms (OR 4.28; 95% CI = 3.02–6.08), and verified ischemic stroke events (OR 2.81; 95% CI = 1.60–4.92). The study also described that other headaches with aura were also significantly associated with stroke symptoms (OR 3.68; 95% CI = 2.26–5.99) and TIA symptoms (OR 4.53; 95% CI = 3.08–6.67).

42.5. Risk of ischemic stroke with non-specific headache

The relationship between non-specific headache and increased stroke risk is inconsistent and is briefly discussed below. In a prospective cohort study of 35,056 Finish men and women aged 25–64, a survey showed that men with chronic unspecified headache had a four-fold higher risk of stroke as compared to those without headache during the first 12 months of follow-up (Jousilahti et al., 2003). The headache (non-specific) associated hazard ratio of stroke was 4.08 (95% CI = 2.1–7.93) at 1-year follow-up in men, and decreased to 1.86 and 1.24 at 5 years and 23 years follow-up respectively. This study did find an increased but statistically non-significant risk of stroke in women, which was explained on the basis of higher prevalence and varied etiology of the non-specific headache in women. Similarly, the hemorrhagic stroke incidence also tended to be higher but did not reach statistical significance due

to the small number of cases. The study concluded that chronic unspecified headache was an independent predictor of stroke among men. The issue of migraine headache was not discussed directly.

The US National Health and Nutrition Examination Survey (NHANES) was another epidemiological study, which showed a strong association of stroke with severe headache and migraine in both women and men (Merikangas et al., 1997). It showed a five-fold increase in stroke in the headache group of younger than 45 years age than those in the no-headache group (3.6% versus 0.7% for men; 2.2% versus 0.4% for women). The risk of stroke related to headache decreased with increasing age. They also raised the possibility of an increased risk attributable to the medications used to treat the headache such as aspirin, acetaminophen, and ergots, but no conclusive evidence was provided.

The Women's Health Study failed to show any association between non-migraine headache and ischemic stroke (Kurth et al., 2005). Similarly the Physician's Health Study did not find any link between ordinary non-migraine headache and subsequent stroke (Buring et al., 1995). The Atherosclerosis Risk in Communities Study failed to show any consistent or significant association between migraine without aura or other headaches without aura and cerebral ischemia symptoms (Stang et al., 2005).

42.6. Risk of hemorrhagic stroke with migraine

There is no clear evidence to suggest that there is an association between unspecified headache or migraine, and hemorrhagic stroke. The Finnish Prospective Observational Cohort Study, which surveyed approximately 35,000 people, showed an increased trend of hemorrhagic stroke which did not reach statistical significance (Jousilahti et al., 2003). Similarly the Physician's Health Study included too few hemorrhagic strokes to evaluate this end-point (Buring et al., 1995). The Women's Health Study was another study that did not show any relationship between migraine and hemorrhagic stroke (Kurth et al., 2005).

In the European Multicenter WHO Collaborative Study, family history of migraine, with or without a personal history of migraine was independently associated with an increased odds ratio of 3.62 (95% CI = 1.37–9.58) and 2.22 (95% CI = 1.26–3.90) for ischemic and hemorrhagic stroke respectively (Chang et al., 1999). However there was no significant increase in the incidence of hemorrhagic stroke in women with personal history of migraine. In a multicenter, population-based, case-control study by Carter et al. (2005) no association was detected in patients who had recurrent headaches or migraines and subarachnoid hemorrhage.

42.7. Clinical features

Migraine can have both positive (flickering lights or spots, paresthesia) as well as negative (loss of vision, numbness) symptoms and it may not be easy to differentiate between an aura and cerebral ischemia presenting as either a TIA or early stroke symptoms. The situation is more complicated in migraine variants of hemiplegic migraine (familial or sporadic), basilar-type migraine, ophthalmoplegic migraine (now called cranial neuralgia), retinal or ocular migraine, migrainous vertigo, aura without headache, and aura with acute onset. The gradual development and expansion of symptoms, with a mix of positive as well as negative features (in general positive more than negative symptoms) lasting less than 60 minutes, are the cardinal features of an aura, whereas the sudden mode of onset and negative symptoms are the hallmark of cerebral ischemia. However the clinical picture may not be as clear in some cases, especially in elderly individuals where one condition may masquerade as the other (Fisher, 1980; Wijman et al., 1998).

42.8. MRI findings

People with migraine are known to have increased incidence of white matter lesions and silent brain infarctions of a lacunar type. These are usually non-specific T2-weighted and FLAIR (fluid attenuated inversion recovery) white matter hyperintensities seen in both the supra- as well as infratentorial compartments. Several studies have shown increased white matter lesions in the brains of migraine patients (Igarashi et al., 1991; Fazekas et al., 1992; De Benedittis et al., 1995; Swartz and Kern, 2004). These lesions are significantly more common in the posterior circulation, an area which has been implicated with strokes in migraineurs (Kruit et al., 2005).

The Cerebral Abnormalities in Migraine an Epidemiological Risk Analysis (CAMERA), an MRI substudy of the Dutch population-based Genetic Epidemiology of Migraine (GEM), reported that people who have migraine with aura had a 12-fold increased risk of cerebellar infarcts (adjusted OR 13.7; 95% CI = 1.7–112) (Kruit et al., 2004). This risk increased, with the increased frequency of migraine attacks of 1 or more attack per month (OR 15.8; 95% CI = 1.8–140). The female subgroup of migraineurs had a higher load of deep white matter lesions (DWML) compared to controls (OR 2.1; 95% CI = 1.0–4.1) and this also

increased with higher attack frequency. A subsequent study by Kruit et al. based on the same population group showed an increased prevalence of infratentorial (predominantly pontine) hyperintensities in the migraineurs (Kruit et al., 2006). They hypothesized that the underlying mechanism may be small-vessel disease (arteriosclerosis), repetitive perfusion deficits, or both.

42.9. Pathogenesis

As discussed above, migraine- or headache-causing stroke can be envisioned in relation to two main scenarios: first, when stroke occurs as part of a prolonged migraine aura (migrainous infarction); and second, when stroke occurs in a migraineur or headache sufferer who has past history of migraine, and the stroke occurs separated in time from a migraine or headache attack (migraine-related stroke). In the second scenario the relationship may be coincidental or causal, whereas in the first case the cause and effect relationship is more robust. The incidence of true migrainous infarction is very low; however, it is this second category that is relatively more common and can be observed in cases where migraine is present with other well-established stroke risk factors or with the rare or questionable stroke risk factors, and have either an independent or synergistic role in the pathogenesis of stroke.

Several mechanisms have been postulated for migraine-causing stroke including: abnormalities of the vasculature (vasospasm and regional blood flow variations) (Henrich, 1987; Rothrock et al., 1988; Welch and Levine, 1990; Olesen et al., 1993; Woods et al., 1994); arterial dissection (Buttinelli et al., 2001; Tzourio et al., 2002b); small-vessel disease (Jousilahti et al., 2003; Kruit et al., 2006); livedo reticularis (Tietjen et al., 2002 a,b); moyamoya (Park-Matsumoto et al., 1999); hereditary or genetic risk factors (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy [CADASIL]) (Tournier-Lasserve et al., 1991; Chabriat et al., 1995; Hutchinson et al., 1995); mitochondrial myopathy, encephalopathy, lactacidosis and stroke (MELAS), and other mitochondrial abnormalities (Montagna et al., 1988; Ohno et al., 1997); MTHFR C677T gene mutation (Scher et al., 2006); autosomal dominant vascular retinopathy, migraine, and Raynaud's phenomenon (Terwindt et al., 1998); hereditary hemorrhagic telangiectasia (HHT) (Steele et al., 1993; Thenganatt et al., 2006); hypercoagulable state (platelet aggregation) (Kalendovsky and Austin, 1975; D'Andrea et al., 1994; Zeller et al., 2004); endothelial abnormalities, release of prothrombotic factors or vasoactive peptides (Ferrari et al., 1989; Ridker et al., 1994; Soriani et al., 1998; Hering-Hanit et al., 2001); elevated von Willebrand factor (Tietjen et al., 2001); antiphospholipid antibodies (Levine et al., 1987; Silvestrini et al., 1994; Straube et al., 1998); cardio-embolic factors (patent foramen ovale and atrial septal aneurysm) (Lechat et al., 1988; Wilmshurst et al., 2000; Wilmshurst and Nightingale, 2001; Lamy et al., 2002); mitral valve prolapse (Petty et al., 1994); abnormal activity of serotonergic Raphe cells leading to hyperexcitability (Eggers, 2001); and interaction with other well-established stroke risk factors (smoking (Scher et al., 2005), hypercholesterolemia (Scher et al., 2005), hypertension (Scher et al., 2005), oral contraceptive pills (Hannaford et al., 1994; Bousser et al., 2000).

Migraine is not considered a primarily vascular disorder but rather a neurovascular process with a primary problem thought to be neural dysfunction of the brainstem and diencephalic nuclei (Goadsby et al., 2002). Although the pain of migraine is attributed to vascular dilatation and meningeal and perivascular nociceptor activation, the aura of the migraine is now considered to be related to the cortical spreading depression of Leao seen in animals (Leao, 1944). It is characterized by a slow wave of neuronal activation followed by decreased cortical activity traversing at a rate of a few millimeters per minute. During this phase of cortical spreading depression it is observed that cortical blood flow decreases correspondingly (Woods et al., 1994). It is also reported that this wave of oligemia is preceded by a transient wave of hyperemia, and is probably the cause of the clinical symptoms of flashing, bright, and jagged lights. Thus the phenomena of hyperemia and oligemia are closely intertwined with aura symptomatology, and during a migrainous infarction it is probably this wave of oligemia that reaches a critical level to cause an infarction.

CADASIL is a disorder of small vessels of the brain characterized by migraine with aura, recurrent subcortical infarcts, and vascular dementia. Migraine with aura is present in one-third of cases and usually the first symptoms preceding the subcortical strokes and behavioral changes by many years. More than half of the cases have atypical migraine auras. The underlying genetic abnormality is a mutation in the NOTCH3 gene. MELAS, a mitochondrial disorder, is associated with frequent migraine attacks and mitochondrial gene mutations. Migraine is also present in many other mitochondrial disorders. Similarly, hereditary hemorrhagic telengiectasia and autosomal dominant vascular retinopathy, migraine and Raynaud's phenomenon, and leptomeningeal angiomatosis (Sturge–Weber syndrome) are other disorders with a genetic or hereditary component leading to changes of vessel walls in small vessels and clinical co-occurrence of stroke and migraine.

Patent foramen ovale (PFO), now an established stroke risk factor, is 2–3 times more common in patients suffering from migraine with aura (Lechat et al., 1988; Lamy et al., 2002). Similarly migraine with aura is twice as common in stroke patients who have presence of a PFO, compared to those who did not have a PFO. Some studies have even shown that closure of the PFO results in a reduction of migraine attacks (Wilmshurst et al., 2000). It is postulated that the left-to-right shunt seen in these patients and those with HHT may result in paradoxical emboli and bypassing of some vasoactive and toxic substances to the intracranial circulation.

Platelet activation and neurogenic inflammation have been implicated in the pathophysiology of migraine. Platelet activation results in increased cytokine production leading to a sterile inflammatory process. A similar mechanism has also been observed with the atherothrombotic process of ischemic stroke. In a case-control study of migraineurs, increased platelet leukocyte aggregation and platelet activation was observed in patients who had migraine with aura, suggesting platelet leukocyte interaction as one of the possible mechanisms of ischemic stroke in these patients (Zeller et al., 2004).

In a case-control study migraine was strongly associated with cervical artery dissection compared to other causes of ischemic stroke (OR 3.6, 95% CI = 1.5–8.6) and the risk was further increased in those who had multiple dissections (OR 6.7) (Tzourio et al., 2002b). It is hypothesized that abnormalities of the vessel wall and its extracellular matrix play a role in the pathogenesis. This is supported by the fact that some migraine patients have elevated serum elastase levels.

Tietjen et al. (2002 a,b) in their recent study reported that more than 20% of their headache clinic population has livedo reticularis, a violaceous reticular mottling of skin secondary to small and medium vessel narrowing at the dermis–subcutis border. They also report a higher frequency of stroke in this cohort of patients. They speculate that a slowly progressive cerebral vasculopathy may be the underlying disorder causing both stroke and migraine in these patients.

Serotonergic 5HT 1_B1_D receptor agonist drugs (triptans), used for treating migraines, have been implicated in causing reversible cerebral vasoconstriction (Meschia et al., 1998). Use of these and other serotonergic agents (like antidepressants, decongestants, diet pills, amphetamines, St. John's wort, and drugs of abuse such as cocaine, ecstasy, methamphetamine) in combination have been reported to cause strokes (Conde Lopez et al., 1998; Singhal et al., 2002). However the data is too scarce to establish a concrete causal relationship.

Stroke incidence is also increased in patients who suffer from migraine and have other underlying established vascular risk factors like hypertension, dyslipidemia, or smoking. A Dutch study had shown that patients with migraine with aura had abnormal cholesterol profile, high blood pressure, and high Framingham risk score for coronary artery disease (Scher et al., 2005).

42.10. Summary

Although considered a chronic episodic disorder, in reality migraine may be a chronic progressive disorder based on the findings of subclinical and silent infarcts and white matter lesions seen on MRI in several studies. It is prudent to identify the population of migraine patients who are at increased risk of ischemic stroke. Migraine patients in the general population should address the control of well-known stroke risk factors such as hypertension, hypercholesterolemia, diabetes mellitus, contraceptive pill, obesity, and smoking. Migraineurs should be treated with prophylactic therapy (pharmacologic or non-pharmacologic) to reduce the frequency of migraine attacks if they occur frequently.

Triptans and ergotamines used for the treatment of migraine are contraindicated in patients with hemiplegic migraine, basilar-type migraine, patients with other vascular risk factors including prior history of stroke, TIA, myocardial ischemia, and angina. It is also recommended that the patients who have two or more stroke risk factors like hypertension, diabetes mellitus, smoking, hypercholesterolemia, or obesity should avoid using triptans unless they have a cardiac evaluation. The prophylactic use of beta blockers has also been implicated in causing stroke and some headache specialists do not use these agents in patients having migraine with prolonged aura or basilar-type migraine due to the concern of limiting the compensatory vasodilatory capacitance (Evans and Lipton, 2001). Women with migraine without aura and no other risk factors for stroke may use a pill with low-dose estrogen (less than 50 μm as per the American College of Obstetricians and Gynecologists [ACOG] guidelines or less than 35 μm as per the World Health Organization [WHO] guidelines). However, the frequency and severity of migraines should be monitored (Petitti, 2003).

Migraine and headache have a bidirectional relationship, acting as a cause or consequence of one another. Migraine in particular and headache in general are now established as independent risk factors for ischemic stroke (Welch, 1994; Tietjen, 2000; Fisher, 2003). This is particularly true for women under the age of 45, who have migraine with aura,

use oral contraception, smoke, and suffer from hypertension. This subgroup should be educated and advised to use the alternate method of contraception and discontinue smoking. Women with migraine without aura should be advised to use low-estrogen oral contraceptive pills. People with a higher frequency of migraine attacks should be on prophylaxis as increased frequency of migraine attacks is associated with abnormalities of white matter lesions on MRI studies. Physicians should be aware of the focal neurological signs and symptoms associated with aura and the increased risk relationship between migraine and stroke, to avoid confusion and dismissing such signs as trivial. Further studies are needed to answer the questions such as whether migraine with aura is a different disease process than migraine without aura, whether migraine is a progressive disorder, whether to abandon the use of oral contraceptives in migraine population, whether to consider closure of patent foramen ovale in patients with migraine, whether to use stroke prophylaxis with antiplatelet agents along with migraine prophylaxis in these patients, should triptans be contraindicated in migraineures with silent brain infarctions or lesions, and whether ischemia is the initial event leading to cortical spreading depression and migraine.

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Chapter 43

Infections and stroke

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Stroke is one of the many clinical manifestations of infectious diseases. Viral, spirochetal, bacterial, fungal, parasitic, mycoplasmal, and rickettsial infections may cause cerebrovascular complications when intracranial vessels are affected by either the microorganisms themselves or by the inflammatory reaction that their presence induces within the nervous system. Alternatively, some remote infections may cause stroke as the result of the activation of pro-thrombotic mechanisms or when, after their effect of the heart, a cardiogenic brain embolism occurs. Cerebrovascular complications of infectious diseases may be ischemic or hemorrhagic, and may range in severity from asymptomatic to fatal. Infectious-related strokes should be diagnosed only after other potential causes of stroke have been excluded, since the presence of a given infection may only provide circumstantial evidence for causality, particularly in areas where those infections are endemic.

43.1. Viral infections

43.1.1. Human immunodeficiency virus (HIV)

A possible association between HIV infection and stroke has been noted since the earliest reports of neurological manifestations of AIDS, where it was suggested that these patients have an increased risk for developing both ischemic and hemorrhagic cerebrovascular complications (Mizusawa et al., 1988; Engstrom et al., 1989). Thereafter, two controlled studies showed no significant differences in the prevalence of stroke among HIV-infected and non-infected individuals (Berger et al., 1990; Hoffmann et al., 2000). This data was in contrast with that found in more recent population-based studies, where it was demonstrated that the relative risk of stroke was highly increased in HIV-infected children and adults who met AIDS diagnostic criteria (Patsalides et al., 2002; Evers et al., 2003; Cole et al., 2004). This high risk persisted even after other identifiable causes of stroke (including opportunistic infections) were excluded, suggesting that HIV by itself may be related to the development of cerebral infarctions or hemorrhages in the setting of advanced immunosuppression. HIV may cause a stroke by inducing either a direct vasculopathy or a hypercoagulable state (Berger, 2004). The former may be responsible for the high prevalence of intracranial aneurysms seen in these patients (Patsalides et al., 2002; Crevits et al., 2005). Combined anti-retroviral therapy including protease inhibitors may accelerate the development of atherosclerosis by inducing dyslipidemia (Malavazi et al., 2004). This could be another risk factor for ischemic stroke in AIDS patients that should be considered in further studies trying to assess the actual role of HIV as a cause of stroke.

43.1.2. Varicella zoster virus (VZV)

VZV may cause two different diseases, varicella and herpes zoster. Varicella results from primary infection with VZV, and herpes zoster is a delayed complication related to the ability of the virus to establish itself in sensory ganglia. Neurologic complications of varicella include cerebellar ataxia, meningitis, transverse myelitis, and ischemic stroke. Cerebral infarctions result from a diffuse or localized vasculopathy. Indeed, cerebral angiography or magnetic resonance angiography (MRA) in some of these patients have shown segmental narrowing of major intracranial arteries, suggesting that the mechanism of arterial damage is direct viral invasion of the vessel walls (Alehan et al., 2002; Kimura et al., 2002).

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Some patients with herpes zoster involving the ophthalmic branch of the trigeminal nerve develop contralateral hemiplegia (Bourdette et al., 1983; Nogueira and Sheen, 2002). In most cases both the cerebral infarction and the herpes zoster occur in the same side, suggesting that the pathogenetic mechanism underlying the infarction is an angiitis related to direct spread of VZV from the trigeminal nerve to major branches of the ipsilateral carotid artery. Other patients develop occlusion of contralateral intracranial blood vessels and bilateral infarctions (Hilt et al., 1983). It is possible that immunosuppression predisposes to the development of a widespread vasculopathy in such cases (Gilden et al., 2002).

Cerebral infarctions may also occur in patients with herpes zoster affecting nerves other than the trigeminal. In some cases there is a direct relationship between the location of the herpetic lesions and the affected vessel, while in others, disseminated or remote skin lesions have been associated with the development of a multifocal intracranial vasculopathy (Gilden et al., 2002). Cerebral infarctions may eventually occur in patients with "zoster sine herpete" (Ahmad and Boruchoff, 2003; Russman et al., 2003). VZV may also be responsible for the development of intracranial hemorrhages related to the rupture of mycotic aneurysms, occurring as the result of an inflammatory necrosis of the vessel walls induced by the virus (Fukumoto et al., 1986).

43.1.3. Viral hemorrhagic fevers

Infections by arenaviruses, phleboviruses, bunyaviruses, flaviviruses, filoviruses, and hantaviruses may induce the development of systemic and intracranial hemorrhages by a combination of pathogenetic mechanisms, including increased vascular permeability, thrombocytopenia, and disseminated intravascular coagulation (Schnittler and Feldmann, 2003). Some of these diseases are mosquito-born, while others are transmitted by rodents, ticks, non-human primates, or by direct human-to-human contagion (Table 43.1).

Table 43.1

Viral hemorrhagic fevers

Disease	Etiology	Transmission	Clinical manifestations	Geographical distribution
Argentine and Bolivian hemorrhagic fevers	Arenavirus (Junin and Machupo virus)	Rodent-born	*Incubation*: 7–14 days *Early*: fever, myalgia, skin rash, ocular pain, petechias in axillae *Late*: hemorrhagic diathesis, encephalopathy	Argentina and Bolivia
Crimean-Congo hemorrhagic fever	Bunyavirus (CCHF virus)	Tick-born	*Incubation*: 2–9 days *Early*: fever, myalgia, headache, conjunctival injection, sore throat. *Late*: hemorrhagic diathesis, encephalopathy	Africa, Eastern Europe, Middle East, China
Dengue hemorrhagic fever	Flavivirus (Dengue virus)	Mosquito-born	*Incubation*: 2–7 days *Early*: fever, myalgia, headache, flushing, abdominal pain *Late*: hemorrhagic diathesis, liver failure, circulatory collapse, myocarditis, encephalopathy	Central and South America, South East Asia, India, Africa
Ebola and Marburg virus infections	Filovirus (Ebola and Marburg virus)	Non-human primates to human	*Incubation*: 5–14 days *Early*: fever, myalgia, headache, arthralgia, conjunctival injection, bradycardia, sore throat, skin rash *Late*: uveitis, hemorrhagic diathesis, encephalopathy	Central Africa

Hantaviral hemorrhagic fever	Bunyavirus (Hantaviruses)	Rodent-born	*Incubation*: 14–21 days *Early*: fever, headache, flushing, conjunctival injection, bradycardia *Late*: hemorrhagic diathesis, renal failure, encephalopathy	Asia, Europe
Kyasanur forest disease, Omsk, Alkhurma and Novosibirsk hemorrhagic fevers	Flavivirus (KFD, OHF, and AHF virus)	Tick-born	*Incubation*: 7–14 days *Early*: fever, myalgia, headache *Late*: hemorrhagic diathesis, encephalopathy	India, Siberia, and Saudi Arabia
Lassa fever	Arenavirus (Lassa virus)	Rodent-born	*Incubation*: 7–18 days *Early*: fever, myalgia, headache, sore throat, pleural effusions *Late*: respiratory distress, hemorrhagic diathesis, encephalopathy	West Africa (Nigeria, Liberia, Sierra Leone)
Rift Valley fever	Phlebovirus	Mosquito-born	*Incubation*: 2–6 days *Early*: fever, myalgia, headache, vomiting, skin rash, sore throat *Late*: retinitis, hemorrhagic diathesis, encephalopathy	Rift Valley (Kenya), Yemen, Saudi Arabia
Yellow fever	Flavivirus	Mosquito-born	*Incubation*: 3–6 days *Early*: fever, myalgia, headache, vomiting, jaundice, bradycardia *Late*: renal and hepatic failure, hemorrhagic diathesis, encephalopathy	Tropical areas of South America and Africa

After a brief incubation period, these conditions proceed with various combinations of fever, headache, myalgias, sore throat, skin rash, echymoses, gingival or gastrointestinal bleeding, and respiratory dysfunction. These diseases usually progress to involve the nervous system where they produce an acute encephalopathy associated with delirium, stupor, coma, and seizures (Cummins, 1991; Isaacson, 2001; Lednicky, 2003; Malavige et al., 2004). Overt stroke syndromes are uncommon, but most patients have pathological or neuroimaging evidence of intracranial bleeding.

Diagnosis of viral hemorrhagic fevers is based on virus isolation or detection of specific antibodies in serum in the proper epidemiological context. Therapy includes supportive measures and correction of coagulation problems. The antiviral agent ribavirin has been used with success in some patients with Lassa fever and Crimean-Congo hemorrhagic fever (Cummins, 1991; Whitehouse, 2004).

43.1.4. Viral encephalitis

A number of viruses causing encephalitis induce inflammatory changes in the walls of small intracranial arteries leading to cerebral infarctions and hemorrhages. The agent of Japanese B virus encephalitis causes bilateral lesions in the thalamus and striatum. Recent studies using a diffusion weighted imaging (DWI) and apparent diffusion coefficient (ADC) map, suggest a vascular nature of these lesions, at least during acute disease (Prakash et al., 2004). Indeed, parenchymal brain hemorrhages probably related to the rupture of small penetrating arteries in an advance state of necrosis may occur in these patients (Sarkar et al., 2005). Ischemic lesions deep in the brain parenchyma have also been reported in patients with measles, Epstein–Barr virus, Nipah virus, Murray Valley, and even in those with West Nile virus encephalitis (Einsiedel et al., 2003; Johkura et al., 2003; Lee et al., 2003; McCarthy, 2003; Rosas and Wippold, 2003). Cerebral ischemic or hemorrhagic lesions may also occur in

patients with herpes simplex virus infections of the brain (Politei et al., 2003).

43.1.5. Systemic viral infections

Remote viral infections, most often located in the respiratory or gastro-intestinal tracts, may put individuals at an increased risk for ischemic stroke (Ribai et al., 2003; Field et al., 2004; Mandrioli et al., 2004). Pathogenetic mechanisms by which systemic viral infections cause stroke are not fully understood, but it has been suggested that a procoagulant state related to increased levels of cytokines, fibrinogen, and other acute phase reactants, or to a decreased activity of proteins C and S, could account for this association (Emsley and Tyrrell, 2002).

43.2. Spirochetal infections

43.2.1. Leptospirosis

Leptospirosis is caused by *Leptospira interrogans*. This zoonotic disease is common in urban centers of Asia and Latin America, and is acquired when humans come into contact with the urine of infected animals or by exposure of the skin or mucous membranes to contaminated water or soil (Bharti et al., 2003). An endotoxin elaborated by this spirochete is responsible for the clinical manifestations of leptospirosis. Its toxic effects may cause acute tubular necrosis, hemorrhagic diathesis, vasculitis, myocarditis, meningitis, and uveitis. Weil's syndrome is a severe form of the disease, characterized by fever, jaundice, renal failure, and hemorrhages in different organs, particularly in the lungs. Some patients develop brain hemorrhages as a result of the bleeding diathesis (Murali et al., 2002; Theilen et al., 2002). Leptospiral infections also cause angiitis of intracranial vessels that may, in turn, cause progressive narrowing of cerebral arteries with the development of an exuberant network of collaterals resembling that seen in patients with moyamoya disease (Shi et al., 1989; Matsushima et al., 1997).

Diagnosis is confirmed by isolation of the causal agent in blood or urine cultures, or by demonstration of a four-fold rise in antibodies titers. Neuroimaging studies may reveal intracranial hemorrhages, cerebral infarctions, or the development of the collateral vessels network already described. Penicillin or doxycycline are effective against *L. interrogans*, but have no effect on the cerebrovascular complications of the disease (Murali et al., 2002). Patients with angiitis should be treated with corticosteroids, and those with intracranial hemorrhages may need vitamin K replacement if the prothrombin time is prolonged.

43.2.2. Lyme disease (borreliosis)

Lyme disease is caused by *Borrelia burgdorferi*. It is a tick-borne disease initially characterized by a skin lesion known as erythema chronicum migrans, which may be followed by neurological manifestations or arthritis. Infections acquired in Europe are more severe and more often associated with cerebral involvement than those acquired in North America (Barbour et al., 1985). Neurological manifestations may occur early in the course of the disease or in the late chronic phase, and include lymphocytic meningitis, encephalitis, myelitis, stroke, optic neuritis, cranial nerve palsies, peripheral neuropathy, and myositis (Nachman and Pontrelli, 2003; Stanek and Strle, 2003). Brain damage may be related to either a direct toxic effect of the causal agent or to the host's immune response against the infection.

Cerebral infarctions in Lyme disease are caused by a segmental obliterative inflammatory vasculopathy affecting small, medium-size, and large intracranial arteries. These may be located in the carotid or vertebrobasilar territories, and may occur as the sole manifestation of the disease or in association with other neurological complications, most often a lymphocytic meningitis (Wilke et al., 2000; Klingebiel et al., 2002; Romi et al., 2004). In such cases, cerebrospinal fluid examination shows inflammatory changes associated with intrathecal production of specific antibodies (Heinrich et al., 2003). CT and MRI allow direct visualization of the infarct, and MRA or cerebral angiography may show segmental arterial narrowing with post-stenotic dilatations, occlusion of multiple branches of the anterior or middle cerebral arteries, or occlusion of the basilar artery (Uldry et al., 1987; Heinrich et al., 2003). Therapy includes doxycycline, ceftriaxone, or penicillin G. These antibiotics may prevent further neurological damage but do not modify the sequelae of pre-existing lesions. Corticosteroids have been used in some patients with stroke-related Lyme disease with various degrees of success (Heinrich et al., 2003; Romi et al., 2004).

43.2.3. Syphilis

Syphilis is caused by *Treponema pallidum*. The infection is transmitted by sexual contact and has become more common during the AIDS epidemic (Chesson et al., 2005). Syphilis is initially manifested by a self-limited genital chancre. Thereafter, secondary syphilitic lesions appear on the skin and mucous membranes. Months to years later, untreated patients develop tertiary manifestations with cardiovascular and cerebral complications. The latter are related to

meningeal inflammation, angiitis, and neuronal degeneration (Roos, 1992). Common manifestations of neurosyphilis include acute meningitis, progressive dementia, tabes dorsalis, and focal deficits resulting from either cerebral infarctions or parenchymal brain gummatous lesions (Timmermans and Carr, 2004).

Syphilitic angiitis is characterized by a proliferative endarteritis with transmural and perivascular infiltration of lymphocytes and plasma cells, subintimal fibroblastic proliferation, and irreversible damage of arterial muscle and elastic fibers. It is called Heubner's arteritis when the process affects medium-sized and large arteries, and Nissl–Alzheimer's arteritis when arteriolar lesions predominate (Saez de Ocariz et al., 1996). Cerebral infarctions occur in about 25% of patients with meningovascular syphilis, and may be associated with memory loss, apathy, irritability, or focal neurological deficits that vary according to the size and location of the infarction (Brightbill et al., 1995). The middle cerebral artery is most often affected, but other intracranial arteries may be affected as well (Gallego et al., 1994; Umashankar et al., 2004). In some cases, cerebral infarctions may occur as the result of remote effects of cardiovascular complications and not due to angiitis (Nakane et al., 1996).

Visualization of *T. pallidum* in cerebrospinal fluid is not possible in most cases. Therefore, diagnosis of neurosyphilis relies on the proper interpretation of serological tests in the context of a suggestive clinical picture (Timmermans and Carr, 2004). Both veneral disease research laboratory (VDRL) and fluorescent treponemal antibody (FTA) have limitations when performed in cerebrospinal fluid. VDRL is highly specific but may be negative in 50% of patients with neurosyphilis. In contrast, the FTA test is associated with a high number of false-positive results (Davis and Schmitt, 1989). Penicillin is the drug of choice for syphilis. Therapy halts the progression of vascular and neuronal damage, but has little effect on pre-existing deficits.

43.3. Bacterial infections

43.3.1. Acute pyogenic meningitis

Haemophilus influenzae, *Neisseria meningitidis*, and *Streptococcus pneumoniae*—the most common pathogens causing pyogenic meningitis—induce the formation of a purulent exudate within the subarachnoid space related to migration of neutrophils and other immune cells (Roos, 2000). Such exudate, together with direct effects of bacterial toxins, may induce changes in subarachnoid blood vessels with the subsequent development of a cerebral infarction. Pathogenetic mechanisms underlying ischemic stroke during the course of acute pyogenic meningitis include: (1) encroachment of large arteries at the base of the brain by a purulent exudate; (2) narrowing of small and medium-sized subarachnoid arteries due to infiltration of the adventitia by inflammatory cells, necrosis of the vessel wall, and disruption of the endothelium; (3) arterial spasm as a remote response to the infection; and (4) direct invasion of cortical veins by bacteria causing septic thrombosis of dural sinuses (Pfister et al., 1992; Chang et al., 2003). Other patients may develop intracranial hemorrhages secondary to the rupture of mycotic aneurysms which, in turn, are related to weakness of the arterial wall caused by extension of the infection through the adventitia (Perry et al., 1992).

Clinical manifestations of cerebrovascular complications of pyogenic meningitis are related to the location and extent of the vascular damage, and are usually associated with common signs and symptoms of the disease, including fever, stiff neck, altered mental status, or intracranial hypertension. Cerebral infarctions most often occur during the first week of the disease and should be promptly diagnosed and treated with corticosteroids to reduce the risk of further vascular damage (Igarashi et al., 1984; Johkura et al., 2002). A spinal tap must be part of the evaluation of all patients with pyogenic meningitis. Cerebrospinal fluid findings include a neutrophilic pleocytosis associated with hypoglycorrhachia and increased protein contents. Gram's stain and cultures permit the identification of the causal agent in 80% of patients. Neuroimaging studies must be performed to rule out the presence of a brain abscess, a subdural or epidural empyema, or thrombosis of intracranial sinuses. New MRI techniques such as DWI are useful to demonstrate acute ischemic lesions that may not be otherwise visible (Fig. 43.1) (Jan et al., 2003). In some cases, control neuroimaging studies performed several months after the acute infection have demonstrated the development of a chronic vasculopathy with progressive intracranial arterial narrowing resembling that seen in patients with moyamoya disease (Czartoski et al., 2005).

43.3.2. Brucellosis

Brucellosis is caused by Gram-negative coccobacilli of the genus *Brucella*, and is acquired by ingestion of unpasteurized goat's milk or dairy products. The acute phase is characterized by fever, chills, and myalgias. In some cases, the disease progresses to affect the nervous system. Clinical syndromes of neurobrucellosis include polyradiculopathy, myelitis, optic neuropathy, and chronic meningitis (Bahemuka et al., 1988; Koussa et al., 2003). Blood vessels may be affected

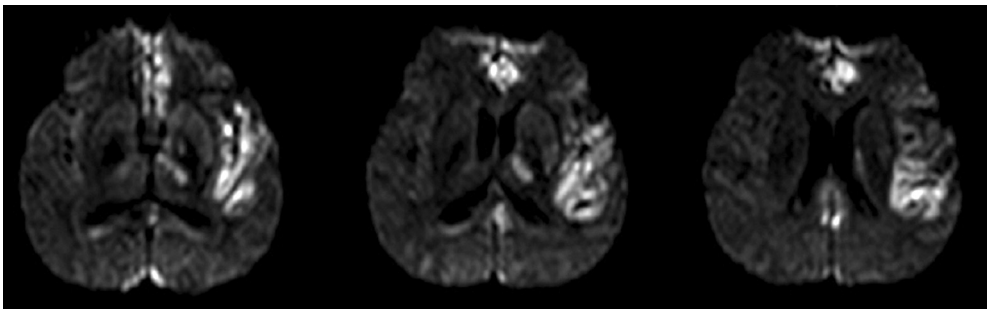

Fig. 43.1. DWI showing multiple areas of cerebral infarction in patient with acute pyogenic meningitis.

by the inflammatory reaction developed within the subarachnoid space in patients with brucella meningitis. Such involvement may cause cerebral infarctions secondary to occlusive angiitis, or subarachnoid hemorrhages due to the rupture of intracranial mycotic aneurysms (McLean et al., 1992). Cerebrospinal fluid examination of patients with meningitis usually include pleocytosis and hypoglycorrhachia. Diagnosis is confirmed by rising serum brucella titers on agglutination tests, by the finding of brucella antigens in the cerebrospinal fluid with the use of PCR, or by recovery of organisms from body fluids, including the cerebrospinal fluid (Al Dahouk et al., 2003; Colmenero et al., 2005). Therapy includes a combination of drugs such as tetracyclines, sulfonamides, rifampicin, or streptomycin, but the neurological deficits related to brain ischemia or hemorrhage are seldom reversible (McLean et al., 1992).

43.3.3. Infective endocarditis

Infective endocarditis is caused by colonization of the endocardium and heart valves by bacteria, rickettsia, fungi and chlamydia. The disease may occur in subjects with prosthetic or native heart valves. In the latter, conditions predisposing to infective endocarditis include congenital and rheumatic heart disease, open heart surgery, mitral valve prolapse, hyperalimentation lines, hemodialysis, and IV drug abuse (Deprele et al., 2004). Endothelial damage, increased platelet aggregation, and thrombus formation are the pathogenetic mechanisms involved in the development of infective endocarditis. Further growth of thrombi result in the formation of nodular vegetations that may be infected. Infected vegetations induce the formation of immune complexes which account for some of the manifestations of infective endocarditis, including systemic vasculitis. Other mechanisms explaining clinical manifestations of the disease are recurrent bacteremia, embolization, and tissue damage. The disease may run an acute or subacute clinical course. Heart failure, meningitis, brain abscesses, and ischemic or hemorrhagic strokes are common presentations of infective endocarditis.

Cerebral infarctions are caused by occlusion of intracranial arteries due to embolic material derived from endocardial vegetations, are most often located in the middle cerebral artery territory, and may have a hemorrhagic component (Chen et al., 2001). Patients with large vegetations as well as those with mitral valve involvement have the highest risk for developing ischemic strokes (Anderson et al., 2003). Embolic material reaching the brain is often contaminated with microorganisms. A brain abscess may therefore develop within the necrotic brain tissue. Intracranial hemorrhages occur in some patients, and may be related to either acute necrotizing arteritis or to the rupture of a mycotic aneurysm (Chukwudelunzu et al., 2002). The former is caused by erosion of the arterial wall due to septic emboli, and may be associated with subarachnoid or multiple parenchymal brain hemorrhages (Fig. 43.2).

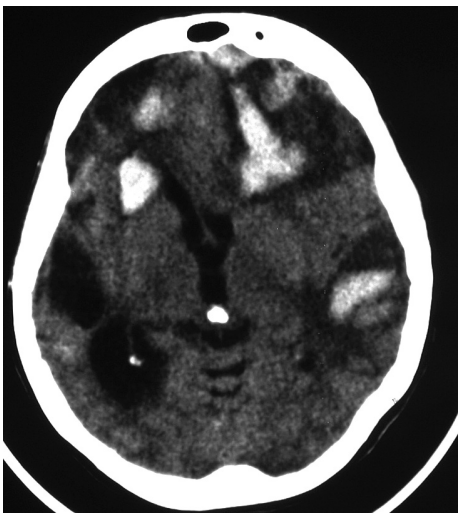

Fig. 43.2. CT showing multiple parenchymal brain hemorrhages in patient with infective endocarditis and necrotizing angiitis of central nervous system.

Mycotic aneurysms may be saccular or fusiform, are usually multiple, and are located in peripheral branches of the anterior or middle cerebral artery; they result from septic embolization to the vasa vasorum or to the arterial wall itself.

Infective endocarditis should be suspected in patients with a predisposing condition that develop fever and a heart murmur. Blood cultures reveal the infective microorganism in about 80% of cases. Echocardiography allows the visualization of vegetations and other cardiac lesions. Antibiotics must be given to eradicate the causal agent. Antiplatelets do not seem to prevent cerebrovascular events in these cases. Surgical valve replacement plays an important role in the management of this condition. There is no specific therapy for acute necrotizing arteritis. Ruptured mycotic aneurysms should be surgically clipped but many unruptured aneurysms disappear with antibiotic therapy (Baddour et al., 2005).

43.3.4. Tuberculosis

Tuberculosis is most often caused by *Mycobacterium tuberculosis*. This acid-fast bacilli enters the body through the respiratory tract, settle in the lungs, and reach the nervous system by the hematogenous route. The first step of brain invasion is the formation of small tubercles within the brain parenchyma, called Rich foci. Then, tubercles may rupture into the subarachnoid space to cause meningoencephalitis or may grow in the brain parenchyma to form tuberculomas (Katti, 2004). Tuberculous meningitis is characterized by the formation of a thick exudate that encroaches subarachnoid blood vessels located at the base of the brain, causing arterial narrowing and cerebral infarctions. Histological changes in these cases include inflammation of the walls of small and medium-sized arteries, fibrinoid and hyaline degeneration of the intima, subendothelial cellular proliferation with narrowing or occlusion of the lumen, and perivascular cuffing of lymphocytes. The inflammatory exudate may induce changes in the walls of cerebral arteries resulting in the formation of mycotic aneurysms (Griffiths et al., 2000). Small blood vessels in and around parenchymal brain tuberculomas may also be infiltrated by inflammatory cells, favoring the occurrence of hemorrhages due to rupture of the involved vessels (Talamás et al., 1989).

Small cerebral infarctions occur in up to 40% of patients with tuberculous meningitis, are most often bilateral, and located in the territory of the lenticulostriate branches of the middle or anterior cerebral arteries, or in the brainstem (Leiguarda et al., 1988; Hsieh et al., 1992; Lan et al., 2001). Large infarctions involving the entire middle cerebral artery territory may also occur. Intracranial hemorrhages are not as common as cerebral infarctions and, as noted, may be related to the rupture of mycotic aneurysms or due to bleeding within parenchymal brain tuberculomas (Talamás et al., 1989; Griffiths et al., 2000).

Diagnosis requires interpretation of data provided by cerebrospinal fluid analysis and neuroimaging studies. In patients with tuberculous meningitis, cerebrospinal fluid shows lymphocytic pleocytosis, low glucose levels, and increased protein contents. Cerebrospinal fluid smears show acid-fast bacilli in less than 50% of cases, but cultures are positive in 80%. Detection of mycobacterial antigens by PCR is of diagnostic value in doubtful cases. CT and MRI usually show hydrocephalus, abnormal leptomeningeal enhancement, and cerebral infarctions (Fig. 43.3) (Ozates et al., 2000). Angiography may show segmental narrowing of cerebral arteries. Diagnosis of intracranial tuberculomas is more complex since they resemble other space-occupying lesions on neuroimaging studies (Salgado et al., 1989). Antituberculous drugs should be started promptly, as any delay in therapy is associated with increased morbidity and mortality. Corticosteroids ameliorate the inflammatory reaction and reduce the risk of angiitis. Patients with a stroke have a high mortality rate, and most survivors are left with permanent sequelae.

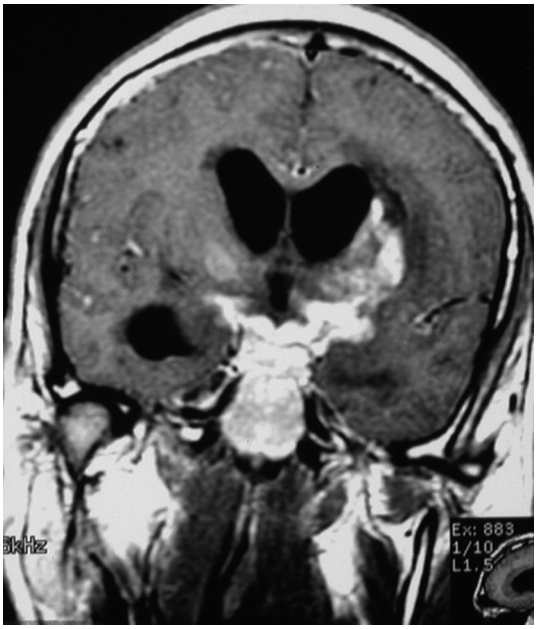

Fig. 43.3. Gadolinium-enhanced MRI showing characteristic findings of tuberculous meningitis, including hydrocephalus, abnormal enhancement of basal leptomeninges, and cerebral infarctions in basal ganglia.

43.3.5. Other bacterial infections

Localized bacterial infections of the ears, orbits, paranasal sinuses, and teeth, may spread to the intracranial cavity to cause occlusion of dural venous sinuses and their cortical veins (Southwick et al., 1986). Infections of the ethmoid and sphenoid sinuses reach the cavernous sinus by contiguity or through emissary veins and produce cavernous sinus thrombosis, which is associated with chemosis, exophthalmos, and ophthalmoplegia (Sanchez et al., 1997). The cavernous segment of the internal carotid artery may be narrowed or occluded with the subsequent development of a cerebral infarction in the carotid territory (Bentham et al., 2004). Chronic otitis media may cause septic lateral sinus thrombosis due to spread of the infection from the mastoid air cells. The disease is characterized by intracranial hypertension without localizing signs, but may be complicated by cerebellar abscesses or cerebellar or temporal lobe venous infarctions. Diagnosis is confirmed by MRI showing hyperintense signals in the thrombosed dural sinuses and hemorrhagic infarctions. Therapy includes antibiotics and anticoagulants in selected cases (Bhatia and Jones, 2002).

Cerebral infarctions during the course of bacterial sepsis are most often related to septic thrombosis of major dural venous sinuses. The diagnosis should be suspected in patients with hemorrhagic infarctions in the subcortical white matter since the superior saggital sinus is the most frequently involved in these cases. The diagnosis is confirmed by MRI and MRA (Fig. 43.4). Septic thrombosis of dural venous sinuses is a life-threatening disease that may be caused by aerobic or anaerobic bacteria. Other patients with septic encephalopathy develop intracranial hemorrhages as the result of disseminated intravascular coagulation (Wijdicks et al., 1994) or multiple ischemic infarctions related to arterial hypotension (Nagaratnam et al., 2002). Recognition of these conditions in patients with sepsis is important to start aggressive therapy with fresh plasma and platelets or to restore cerebral blood flow.

43.4. Fungal infections

43.4.1. Aspergillosis

Aspergillosis is caused by different species of *Aspergillus* (*A. fumigatus, A. terreus, A. flavus*). These are opportunistic pathogens most often affecting immunosuppressed hosts. Cerebral involvement may occur in patients with disseminated disease, and usually takes the form of a necrotizing meningoencephalitis associated with parenchymal brain space-occupying lesions or stroke (Schwartz and Thiel, 1997; DeLone et al., 1999). *Aspergillus* hyphae reach the nervous system by hematogenous spread from a remote foci of infection, and invade small and medium-sized intracranial blood vessels causing coagulative necrosis of the vessel walls. Such necrosis may induce arterial thrombosis with the subsequent development of cerebral infarctions (Roberts et al., 2004), or may cause weakness of the vessel walls with formation of mycotic aneurysms that may rupture causing subarachnoid hemorrhages (Kurino et al., 1994; Hurst et al., 2001; Ho and Deruytter, 2004). In addition, direct extension of the inflammatory process from *Aspergillus* infection of the orbit and paranasal sinuses may result in thrombosis of the cavernous segment of the internal carotid artery (Chandra et al., 2000). Diagnosis is confirmed by demonstration of *Aspergillus*-specific DNA in cerebrospinal fluid or by isolation of the causal agent in culture of tissue specimens (Kami et al., 1999). Mortality of this condition is high; however, some patients had improved after therapy with itraconazole or voriconazole (Schwartz and Thiel, 2004).

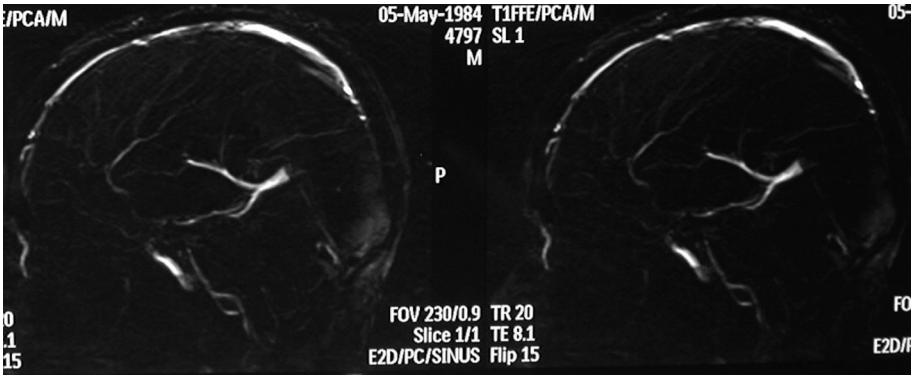

Fig. 43.4. MRA showing massive thrombosis of major intracranial venous sinuses in patient with sepsis. Courtesy of Dr. Jorge Garcés, Guayaquil, Ecuador.

43.4.2. Coccidioidomycosis

Coccidioidomycosis is caused by *Coccidioides immitis*. Humans acquire the infection by inhalation of this fungi. While *C. immitis* may infect normal hosts, immunocompromised individuals are more prone to develop severe disease. *C. immitis* elicits a caseating granulomatous reaction in infected tissues that resembles that observed in tuberculosis. Nervous system involvement occurs in less than 1% of cases, most often in the form of a diffuse arachnoiditis with formation of a thick exudate that predominates in the basal surface of the brain (Fig. 43.5). Entrapment of leptomeningeal blood vessels within this dense exudate may induce angiitis with cerebral infarctions (De Carvalho et al., 1980; Williams et al., 1992; Erly et al., 1999a), or may favor the formation and rupture of mycotic aneurysms with subarachnoid hemorrhages (Erly et al., 1999b). Extension of the inflammatory process to the spinal cord may occlude the anterior spinal artery with subsequent development of an intramedullary infarction. Also, invasion of dural venous sinuses with venous thrombosis and multiple hemorrhagic infarctions may occur (Kleinschmidt-DeMasters et al., 2000).

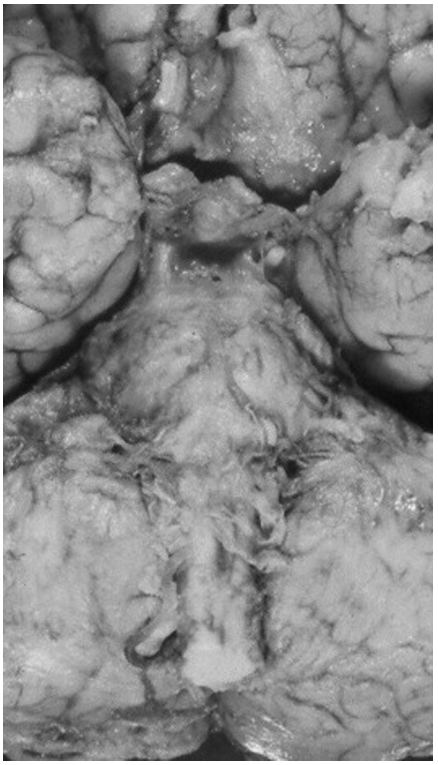

Fig. 43.5. Coccidioidal meningitis. Brain shows diffuse arachnoiditis with entrapment of cranial nerves arising from brainstem and leptomeningeal blood vessels.

Diagnosis rests on the demonstration of fungi in body fluids or deep tissue biopsy. Cerebrospinal fluid cultures are positive in less than 50% of patients with nervous system involvement. Immune diagnostic tests allow the detection of specific antibodies in 90% of patients. Cerebrospinal fluid findings in patients with meningitis include pleocytosis, increased protein levels, and decreased glucose levels. Neuroimaging studies show enhancement of leptomeninges, hydrocephalus, and infarctions in the territory of small perforating branches of the middle cerebral artery (Erly et al., 1999b). X-ray films of the chest are most often abnormal, showing cavitations, nodules, and miliary lesions (Bronnimann et al., 1987). Patients with coccidioidal meningitis should be treated with fluconazole associated with intravenous and intrathecal amphotericin B.

43.4.3. Cryptoccocosis

Cryptoccocosis is caused by *Cryptococcus neoformans*, a yeast found in pigeon excreta and soil that enters the human body through the respiratory tract. While this yeast may cause disease in normal hosts, it has predilection to infect HIV-positive patients and has become a common nervous system pathogen in the AIDS era (Bicanic and Harrison, 2005). Cryptococcal meningitis is characterized by a low-grade fever, headache, personality changes, and lethargy. Some patients develop focal signs related to the formation of parenchyma brain torulomas or to the development of cerebral infarctions related to the inflammatory occlusion of small leptomeningeal vessels secondary to arachnoiditis (Saul et al., 1986; Sung et al., 1991; Weeks and Clough, 1995; Batista Leite et al., 2004). Multiple cerebral infarctions may also result in the development of cognitive decline (Aharon-Peretz et al., 2004). Cerebral infarctions may be located in the carotid or vertebrobasilar territories (Kalita et al., 1999). Diagnosis of cryptococcal meningitis rests on the visualization of the causal agent on Indian ink preparations of cerebrospinal fluid or the demonstration of elevated cryptococcal antigen titers in serum or cerebrospinal fluid. Neuroimaging findings include hydrocephalus, enhancement of leptomeninges, granulomatous mass lesions, and lacunar infarctions (Popovich et al., 1990; Lan et al., 2001). Therapy with amphotericin B associated with fluocytosine and fluconazole is effective in some patients, although the rate of therapeutic failures is still high. Some patients may even develop a stroke after successful clearance of the infection (Lane et al., 2004).

43.4.4. Mucormycosis

Mucormycosis is caused by fungus of the class *Phycomycetes*, genus *Rhizopus*. Intravenous drug abusers as well as patients with conditions predisposing to immunosuppression and those with diabetic ketoacidosis are especially susceptible to develop mucormycosis. The most severe form of the disease is rhinocerebral, in which nervous system involvement is secondary to extension of the infection from paranasal sinuses and orbits. In this form, the cavernous sinus is thrombosed with the subsequent development of occlusion of the intracavernous internal carotid artery (Sugar, 1992). These patients develop cerebral infarctions that may be bilateral when both carotid arteries are affected (Gamba et al., 1986; Kameh et al., 1997). Other intracranial arteries such as the basilar artery or the posterior cerebral arteries may be affected when the infection extends beyond the cavernous sinuses (Calli et al., 1999; Thajeb et al., 2004). Hyphal invasion of blood vessels may also damage their endothelium with the subsequent formation of mycotic aneurysms. *Phycomycetes* may also reach the brain by the hematogenous route causing parenchymal brain abscesses without rhino-orbital disease (Escobar and Del Brutto, 1990). Those lesions may have a hemorrhagic component due to the tendency of *Phycomycetes* to invade cerebral blood vessels (Ginsberg et al., 1987). A high index of suspicion of this condition, on the basis of clinical manifestations and neuroimaging findings, is important since prompt therapy with high doses of amphotericin B may improve the prognosis.

43.4.5. Other fungal infections

In addition to infections already described, a stroke may occur during the course of many other fungal infections of the nervous system. Cerebral infarctions may be related to occlusion of small penetrating arteries as reported in patients with meningitis due to phaeohyphomycosis (Moja et al., 2000), due to dural venous sinus occlusion as described in infections due to *Pseudoallescheria boydii* (Fessler and Brown, 1989), or as the result of a cardiogenic brain embolism as seen in patients with *Histoplasma capsulatum* endocarditis (Wheat et al., 1990). Intracranial hemorrhages also occur and are most often related to the rupture of mycotic aneurysms as described in patients with candidiasis (Rabah et al., 1998; Takeda et al., 1998).

43.5. Parasitic infections

43.5.1. Amebiasis

Cerebral amebiasis is caused by free-living amebae of the genera *Naegleria*, *Acanthamoeba*, and *Balamuthia*. The former causes a fulminating disease called primary amebic meningoencephalitis, whereas *Acanthamoeba* and *Balamuthia* produce a subacute disease called granulomatous amebic encephalitis (Campbell, 1993). *Naegleria* enters the body through the nasal cavity and affects normal hosts, particularly children and young adults. In contrast, *Acanthamoeba* and *Balamuthia* infections most often enter the body through the skin and lungs, and usually affect immunosuppressed individuals.

Patients with *Naegleria* infection develop hemorrhagic necrosis of the frontal and temporal lobes. There is a severe neutrophilic response within the necrotic areas, and multiple trophozoites are found in perivascular spaces, suggesting that brain damage in primary amebic meningoencephalitis is related to an immunological mediated injury of cerebral blood vessels induced by the parasites (Cogo et al., 2004; Okuda et al., 2004). *Acanthamoeba* and *Balamuthia* infections usually result in the formation of hemorrhagic brain abscesses. In such cases, invasion of the walls of intracranial arteries by trophozoites causes a necrotizing vasculitis leading to cerebral infarctions (Griesemer et al., 1994; Schumacher et al., 1995; Zagardo et al., 1997). This inflammatory response may also result in weakness of the vessel walls with formation of mycotic aneurysms (Martinez et al., 1980).

Examination of fresh samples of cerebrospinal fluid can show mobile trophozoites in patients with *Naegleria* encephalitis. In contrast, the diagnosis of *Acanthamoeba* and *Balamuthia* infections rests on the demonstration of parasites in tissue samples (Campbell, 1993). Mortality of these conditions is high despite therapy with amphotericin B or other agents.

43.5.2. American trypanosomiasis

American trypanosomiasis (Chagas' disease) is caused by the protozoan *Trypanosoma cruzi*. The disease is transmitted to humans by the bite of bugs of the genus *Triatoma*, and eventually by blood transfusion or needle-sharing among IV drug abusers. Chagas' disease has three evolutive stages: acute, indeterminate, and chronic (Umezawa et al., 2000). The acute stage is often characterized by an inoculation chagoma located in the orbital region, as well as by myocarditis or encephalitis. During indeterminate and chronic stages, pathological changes of Chagas' disease include megaesophagus, megacolon, and a dilated cardiopathy.

Chagas' disease-related strokes are most often cardio-embolic and occur in patients with congestive heart failure, chronic dilated cardiomyopathy, cardiac arrhythmias (right bundle-branch block and atrial fibrillation), or ventricular aneurysms (Fig. 43.6). The middle cerebral artery territory is the most frequently

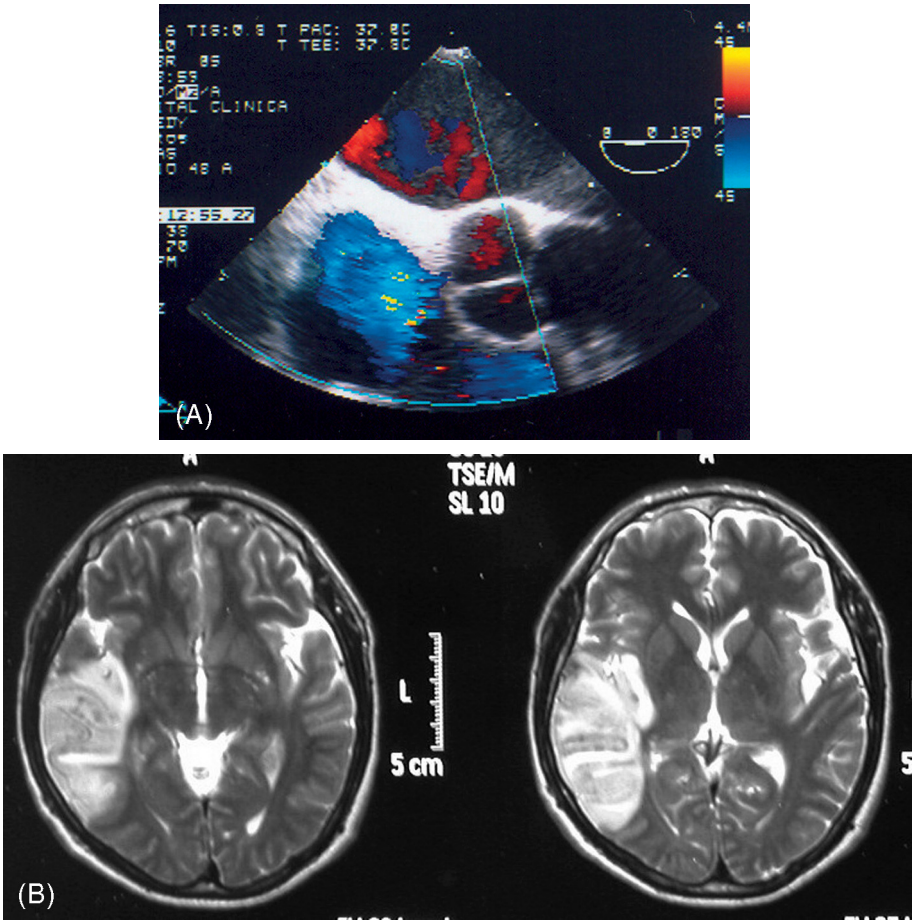

Fig. 43.6. Transthoracic echocardiogram showing dilated cardiomyopathy (A), and T2-weighted showing cortical infarction in middle cerebral artery territory (B) in patient with chronic Chagas' disease.

affected, and infarctions may experience hemorrhagic transformation (Reis Lopes et al., 1991; Carod-Artal et al., 2001, 2003). From 20% to 40% of patients with chagasic myocardiopathy may develop cerebrovascular complications (Aras et al., 2003). Recent studies have shown that cerebral infarctions may also occur in chagasic patients without cardiac abnormalities, suggesting that Chagas' disease-related strokes may also be related to an intracranial vasculopathy directly induced by the parasite (Petkova et al., 2001; Pinto et al., 2002). Diagnosis rests on the demonstration of *T. cruzi* in blood smears or cerebrospinal fluid samples or by serologic testing. Nifurtimox, benznidazole, or itraconazole are useful for patients with acute Chagas' disease and for those with acute reactivations of chronic disease. Secondary stroke prevention with anticoagulants is recommended for patients with cardiac arrhythmias or apical aneurysms.

43.5.3. Coenurosis

Coenurus cerebralis, the encysted larval stage of the dog tapeworm *T. multiceps*, may infect the nervous system. Parasites may be located in brain parenchyma or subarachnoid space at the base of the skull. The latter induce arachnoiditis with obstruction of cerebrospinal fluid transit, and angiitis with cerebral infarctions due to affection of blood vessels arising from the circle of Willis (Hermos et al., 1970). Cerebrospinal fluid examination may show a mild lymphocytic pleocytosis with hypoglycorrhachia. CT and MRI findings include hydrocephalus, cerebral infarctions, and cystic or ring-enhancing lesions located in brain parenchyma or basal cerebrospinal fluid cisterns (Schellhas and Norris, 1985; Pau et al., 1987). Diagnosis must be confirmed by biopsy of a brain lesion; however, even microscopically, it may be difficult to differentiate this condition from cysticercosis and *Coenurus*

cerebralis must be distinguished by the presence of multiple scolices. No drug has proved effective against coenurosis.

43.5.4. Cystic hydatid disease

Cystic hydatid disease is caused by *Echinococcus granulosus*, a parasite of dogs and sheep. Humans acquire the infection by ingesting water or food contaminated with eggs of this tapeworm. Cerebral involvement is most often characterized by a single parenchymal brain cyst that causes focal deficits and intracranial hypertension (Taratuto and Venturiello, 1997b).

Some patients develop ischemic strokes associated with a primary hydatid cyst of the heart. Most infarctions are located in the territory of the middle cerebral artery, and hydatid cysts subsequently develop within the necrotic brain tissue, suggesting that infarctions are related to embolic occlusion of an intracranial artery with fragments of a cyst previously broken within the cardiac cavities (Sierra et al., 1985; Benomar et al., 1994). The diagnosis of cardiac hydatid disease rests on two-dimensional echocardiography, and that of cerebral cystic hydatidosis is made by neuroimaging findings of a large cystic lesion that does not enhance after contrast medium administration (Fig. 43.7). Surgical resection of cardiac lesions is recommended to avoid the risk of embolism, and cerebral cysts may be resected by surgery or may be treated with albendazole (Altinors et al., 2000).

43.5.5. Gnathostomiasis

Gnathostomiasis is caused by *Gnathostoma spinigerum*, a nematode with a complex life cycle involving dogs and cats as definitive hosts, cyclops as first intermediate hosts, and many animal species as second intermediate hosts. Humans are infected by eating undercooked fish, crab or poultry contaminated with larvae of this parasite (Moore et al., 2003). Once ingested, larvae cross the intestinal wall and migrate to subcutaneous tissues and internal organs, including the nervous system. The disease is endemic in Southeast Asia, as well as in Central and South America.

Subcutaneous migration of the larvae leaves painful swelling tracts that are visible to the naked eye (Fig. 43.8). Neurological complications of gnathostomiasis include myelitis, meningitis, and subarachnoid or parenchymal brain hemorrhages, which may occur in 15% to 30% of patients with cerebral involvement. In Thailand, gnathostomiasis is a leading cause of intracranial hemorrhage in children (Visudhiphan et al., 1980). Cerebrospinal fluid examination shows a mononuclear pleocytosis with an increase in protein contents and normal glucose levels; eosinophils are found in the sediment. CT or MRI may show migrating larvae within the brain parenchyma or unusually long or multiple parenchymal brain hemorrhages that may extend into the cervical spinal cord (Sawanyawisuth et al., 2004; Sithinamsuwan and Chairangsaris, 2005). Mycotic aneurysms may be seen in some patients with subarachnoid hemorrhages. Diagnosis is confirmed by identification of the larvae in tissue samples, or by detection of specific serum antibodies by immunoblotting. Autopsy studies have shown the larvae at the end of long hemorrhagic tracts extending from the basal ganglia to the lower brainstem (Chitanondh and Rosen, 1967). There are no studies on medical therapy for cerebral gnathostomiasis and the prognosis depends on the severity and extension of the intracranial bleeding.

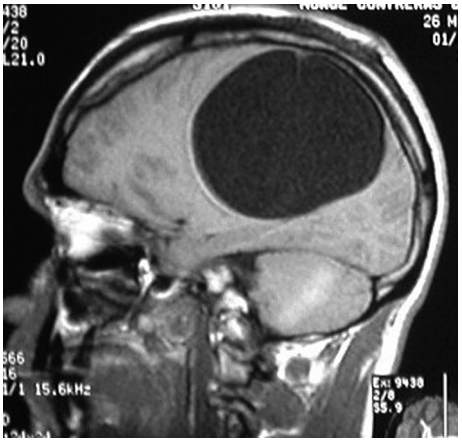

Fig. 43.7. T1-weighted MRI showing huge cystic parenchymal brain lesion in patient with alveolar echinococcosis.

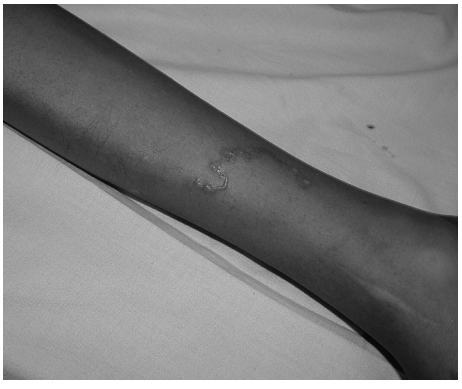

Fig. 43.8. Characteristic appearance of subcutaneous gnathostomiasis.

43.5.6. Lagochilascariasis

Lagochilascariasis is a rare disease caused by the nematode *Lagochilascaris minor*. Opossums and raccoons usually harbor the parasite and humans may acquire the disease by eating undercooked meat from infected animals. Lagochilascariasis usually courses with subcutaneous abscesses on the head and neck. Nervous system involvement may occur as the result of contiguous dissemination of the infection from the subcutaneous tissue through the skull (Pinheiro Veloso et al., 1992). The brain of one patient who was dying from acute encephalopathy related to *L. minor* infection showed multiple areas of hemorrhages and infarction; several adult worms and larvae were found within the necrotic and hemorrhagic tissues, suggesting that parasites induced vascular damage (Rosemberg et al., 1986). There is no known therapy for cerebral lagochilascariasis.

43.5.7. Malaria

Malaria is caused by *Plasmodium falciparum*, and represents a serious health problem for the developing world, killing 3 million people every year. Parasites are inoculated through the skin during a blood meal by a female *Anopheles* mosquito. Parasites are then carried to the liver of the infected host, where they mature and enter the bloodstream to parasitize red blood cells. Patients who die with cerebral malaria have diffuse cerebral swelling, small ring hemorrhages in the white matter of cerebral hemispheres, and plugging of cerebral capillaries and venules by parasitized erythrocytes (Roman, 1991). Ring hemorrhages result from extravasation of erythrocytes due to endothelial damage. Since erythrocytes forming the ring hemorrhages are not parasitized, blood vessel damage may be related to the liberation of vasoactive substances (humoral hypothesis of brain damage). In contrast, plugging of intracranial blood vessels is related to an increased adherence of parasitized erythrocytes to the endothelium, causing obstruction of the cerebral microvasculature (mechanical hypothesis). Since neither the humoral nor the mechanical hypothesis explain the brain damage in cerebral malaria, it is currently accepted that a combination of both factors, together with systemic complications of the disease, explain more satisfactorily the pathogenesis of brain damage than isolated mechanisms (Mackintosh et al., 2004).

Cerebral malaria is an acute condition presenting with headache, seizures, focal neurologic deficits, and somnolence or agitation that rapidly progresses to coma. The disease is often complicated by pulmonary edema, renal failure, hypoglycemia, intravascular hemolysis, and disseminated intravascular coagulation causing intracranial hemorrhages (Murugavel et al., 1989). Focal signs are related to a cerebral infarction due to arterial thrombosis occurring during the acute phase of the disease (Leopoldino et al., 1999). *P. falciparum* is seen by examining blood smears with Giemsa stain. However, repeated examinations may be needed since parasitemia is cyclical. Cerebrospinal fluid examination is normal. Neuroimaging studies may show diffuse brain swelling, cerebral infarctions, or small hemorrhages in severe cases (Cordoliani et al., 1998). Quinine and artemether are the drugs of choice for cerebral malaria (Birbeck, 2004). Corticosteroids are harmful to these patients and should not be used (Warrell et al., 1982). Despite therapy, up to 25% of patients die, and survivors may be left with irreversible neurologic sequelae.

43.5.8. Neurocysticercosis (NCC)

NCC is the most common helminthic infection of the nervous system. It occurs when humans become intermediate hosts in the life cycle of the pork tapeworm *Taenia solium* by ingesting its eggs from contaminated water or food. Once in the human intestinal tract, eggs hatch into oncospheres which, in turn, enter the bloodstream and evolve into cysticerci within the tissues of the host. Cysticerci are located in brain parenchyma, subarachnoid space, ventricular system, and spinal cord. The inflammation around subarachnoid cysticerci induces the formation of a dense exudate composed of collagen fibers, multinucleated giant cells, and parasitic membranes (Pitella, 1997). This causes leptomeningeal thickening with entrapment of cranial nerves and blood vessels arising from the circle of Willis (Fig. 43.9). Cerebral infarctions may occur as the result of inflammatory occlusion of small and medium-sized arteries at the base of the brain, or due to the formation of atheroma-like deposits resulting from endothelium disruption secondary to the inflammatory reaction induced by cysts located near the vessels (Rodriguez-Carbajal et al., 1989; TerPenning et al., 1992; Levy et al., 1995; Kohli et al., 1997). In addition, inflammation may cause weakness of the vessel wall with the subsequent formation of a mycotic aneurysm that may rupture, causing subarachnoid hemorrhage (Huang et al., 2000; Kim et al., 2005).

Stroke is common among patients with subarachnoid NCC, but it is seldom observed in other forms of the disease. In a series of 28 patients with subarachnoid NCC, 15 (53%) had angiographic evidence of angiitis, and 8 had a cerebral infarction (Barinagarrementeria and Cantú, 1998). In another study of 65 patients with NCC-related cerebral infarction, 35 had cystic lesions in the subarachnoid space, and 30 had

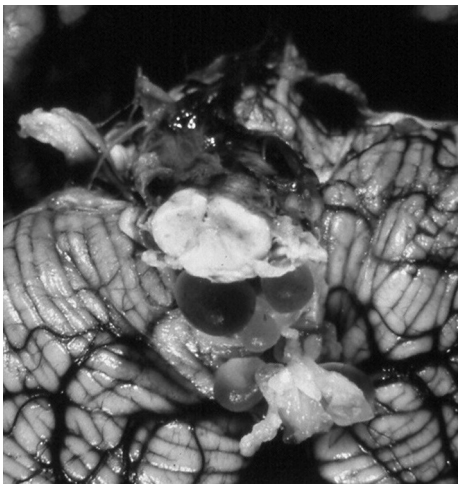

Fig. 43.9. Subarachnoid neurocysticercosis. Cystic lesions and arachnoiditis entrap cranial nerves and blood vessels at the base of the brain.

diffuse arachnoiditis (Cantú and Barinagarrementeria, 1996). Cerebrovascular complications of NCC include: (1) transient ischemic attacks due to narrowing of the intracranial internal carotid artery by a large subarachnoid cyst; (2) lacunar syndromes related to small cerebral infarctions located in the internal capsule or the subcortical white matter; (3) large cerebral infarctions secondary to the occlusion of the anterior or middle cerebral arteries; (4) brainstem infarctions associated with occlusion of branches of the basilar artery; and (5) hemorrhagic strokes related to the rupture of mycotic aneurysms (Del Brutto, 1992).

Diagnosis is possible after interpretation of data provided by neuroimaging studies and results of immunologic tests. CT and MRI show the infarction as well as the characteristic findings of subarachnoid NCC, including abnormal enhancement of leptomeninges, hydrocephalus, and cystic lesions located at the Sylvian fissure or basal cisterns (Barinagarrementeria and Del Brutto, 1989). Angiography or transcranial Doppler may show segmental narrowing or occlusion of intracranial arteries (Cantú et al., 1998). Cerebrospinal fluid analysis shows lymphocytic pleocytosis and increased protein contents. Immune diagnostic tests are a valuable complement to neuroimaging, but they should never be used alone to exclude or confirm the diagnosis (Del Brutto et al., 2001). Therapy depends on the location of parasites and the degree of disease activity. Albendazole destroys most subarachnoid cysts. However, due to proximity of these cysts to intracranial blood vessels, the inflammatory reaction that occurs during cyst destruction may enhance the process of endarteritis (Del Brutto et al., 1992). Dexamethasone must be given to reduce the risk of this complication. For patients with associated hydrocephalus, shunt placement must be contemplated before medical therapy.

43.5.9. Paragonimiasis

Paragonimiasis is caused by trematodes of the genus *Paragonimus*, and is acquired by humans after the ingestion of their larvae in undercooked freshwater crabs or crayfish. Neurological manifestations are rare, and include meningitis, parenchymal mass lesions, or cerebral hemorrhages (Kusner and King, 1993). The latter occur as the result of a necrotizing vasculitis developed during early granuloma formation (Brenes-Madrigal et al., 1982; Medina et al., 1998). The described association of cerebral paragonimiasis with an intracranial aneurysm suggest that chronic meningeal inflammation may favor the development of mycotic aneurysms in some of these patients (Choo et al., 2003). The meningitic form of the disease may also be associated with small cerebral infarctions caused by endarteritis (Oh, 1968). Diagnosis is suggested by the presence of specific antibodies in cerebrospinal fluid or by the finding of multiple confluent calcifications resembling "soap bubbles" on neuroimaging studies (Kang et al., 2000). Further diagnostic support is provided by demonstration of *Paragonimus* eggs in sputum. Therapy includes praziquantel and corticosteroids.

43.5.10. Schistosomiasis

Schistosomiasis is caused by trematodes of the species *Schistosoma*. These parasites enter the body through the skin following aquatic exposure to their larval forms. Then, larvae migrate and settle (as adult worms) in mesenteric veins or the vesical plexus. Neuro-schistosomiasis occurs when larvae ectopically migrate to the spinal cord or the cerebral vasculature (Bill, 2003). All *Schistosoma* spp. induce similar pathologic changes, which are mainly related to the inflammatory or granulomatous reaction developed around parasites. Stroke syndromes occur in a number of patients with neuro-schistosomiasis. The most common cerebrovascular complication is a transverse myelopathy due to inflammatory necrosis of the spinal cord or to occlusion of the anterior spinal artery. Myelopathy affects the lower spinal cord, and is characterized by flaccid paraplegia, sphincter dysfunction, and sensory loss (Scrimgeour and Gajdusek, 1985; Carod Artal et al., 2004). Cerebral infarctions may also occur but are rare. A recently described patient with *S. mansoni* infection-related cardiomyopathy developed multiple cerebral infarctions secondary to cardiogenic brain embolism (Sarazin et al., 2004). Parenchymal brain and subarachnoid hemorrhages have also been

reported (Pompeu and Sampaio de Lacerda, 1979; Preidler et al., 1996). They are related to damage of intracranial arteries induced by the parasites. Such damage includes fibrinoid necrosis of arterial walls with microaneurysm formation, formation of intravascular granulomas with partial destruction of the artery, and intimal thickening with interruption of the internal elastic membrane (Liu, 1993).

Diagnosis of *Schistosoma*-induced stroke requires a high index of suspicion. Cerebrospinal fluid examination usually shows a mononuclear pleocytosis with increased protein contents. Most patients have specific antibodies in serum or cerebrospinal fluid. Absence of *Schistosoma* eggs in stool or urine do not exclude the diagnosis. Corticosteroids ameliorate the process of endarteritis which may cause further brain and spinal cord damage (Fowler et al., 1999).

43.5.11. Sparganosis

Sparganosis is caused by infection with the second-stage larva of *Spirometra mansoni*. Dogs and cats are definitive hosts of this cestode, cyclops are first intermediate hosts, and frogs and snakes are second intermediate hosts. Humans acquire the disease by drinking water contaminated with cyclops harboring the larva (sparganum), by eating infected frog or snake meat, or by applying the flesh of a frog as a poultice to the eye. Once in the human body, the sparganum migrates to subcutaneous tissue, skeletal muscles, or through the foramina of the skull base and vertebral column to invade the nervous system. The sparganum can be located in subarachnoid space, brain parenchyma, or spinal cord (Holodniy et al., 1991). Common findings in cerebral sparganosis are intracranial hemorrhages along the tracks of larvae migration (Wong and Ho, 1994; Jeong et al., 1998). Other patients may present with a cerebral infarction related to the occlusion of an intracranial artery affected by angiitis (Han et al., 2001). Neuroimaging abnormalities usually include multifocal areas of low density within the subcortical white matter, focal cortical atrophy, ipsilateral ventricular enlargement, spotty calcifications, enhancing nodules that may change in location on sequential scans, and intracranial hemorrhages or infarctions (Chang et al., 1992). Diagnosis relies on the direct visualization of the parasite from a brain biopsy. Surgical resection of the parasite is the treatment of choice because there is no specific medical therapy.

43.5.12. Strongyloidiasis

Strongyloidiasis is caused by *Strongyloides stercoralis*. Under normal circumstances this nematode inhabits the human intestinal tract and does not invade the nervous system. However, the hyperinfection syndrome—disseminated strongyloidiasis—may occur when the host's immune mechanisms fail to control its normal cycle of autoinfection (Morgello et al., 1993). In some of these patients, cerebral infarctions may occur as the result of parasitic obstruction of small intracranial blood vessels (Masdeu et al., 1982; Cappello and Hotez, 1993). Diagnosis requires identification of *S. stercoralis* in cerebrospinal fluid or tissue specimens. Mortality of the hyperinfection syndrome is high, although some patients improve with thiabendazole or ivermectin treatment (Zaha et al., 2000).

43.5.13. Trichinosis

Trichinosis is caused by ingestion of undercooked pork meat contaminated with larvae of *Trichinella spiralis*, a disease characterized by fever, myalgia, periorbital edema, and eosinophilia. The heart and the nervous system may be involved in 5% of cases (Clausen et al., 1996). Cerebrovascular complications of neurotrichinosis include hemorrhagic infarctions related to venous thrombosis, and small subcortical infarctions caused by small-artery disease (Gay et al., 1982; Feydy et al., 1996; Gelal et al., 2005). Pathogenesis of trichinosis-induced stroke has been attributed to occlusion of intracranial blood vessels by migrating larval emboli or to hypereosinophilia (Taratuto and Venturiello, 1997a). Eosinophils may induce vascular occlusion through a direct prothrombotic effect or may damage the vascular endothelium after being stimulated by cytokines produced by immunocompetent cells in response to *T. spiralis* infection (Fourestie et al., 1993). Diagnosis is made by demonstration of increased serum antibody titers, or by the identification of parasites in muscles. Corticosteroids are advised to suppress the eosinophilic-induced vascular damage. Various antihelminthic drugs are effective against muscular parasites but their value for patients with neurotrichinosis is uncertain (Watt et al., 2000).

43.6. Other infections

43.6.1. Mycoplasmal infections

Mycoplasmas are microorganisms with special properties related to the lack of a rigid cell wall. The most important human pathogen is *M. pneumoniae*, which usually causes upper respiratory tract infections. Neurological complications of mycoplasmal infections include leukoencephalitis, aseptic meningitis, cranial nerve palsies, peripheral neuropathies, myelitis and stroke, and may occur as a remote complication of

respiratory disease or due to direct invasion of the nervous system by the microorganism (Koskiniemi, 1993; Sotgiu et al., 2003).

Cerebral infarctions are most often located in the territory of the middle cerebral artery and have been related to the development of an autoimmune vasculitis or due to a disseminated intravascular coagulation (Mulder and Spierings, 1987; Fu et al., 1998; Ovetchkine et al., 2002). In addition, some patients with post-infectious leukoencephalitis complicating *M. pneumoniae* infections develop diffuse cerebrovascular lesions—capillary thrombosis, perivascular hemorrhages, perivenular mononuclear infiltrates—as the result of an immune-related vascular damage (Fisher et al., 1983). Mycoplasmal-induced cerebrovascular damage should be suspected in stroke patients with a preceding or concurrent respiratory tract infection in whom cold hemagglutinins are detected in serum. A four-fold rise in antimycoplasmal titers or detection of *M. pneumoniae* DNA in cerebrospinal fluid are required for definitive diagnosis (Padovan et al., 2001). As much of the brain damage is due to an autoimmune process, therapy with erythromycin or tetracycline does not alter the course of the neurological complications of mycoplasmal disease.

43.6.2. Rickettsial infections

Rickettsial infections are insect-borne diseases caused by a family of obligate intracellular Gram-negative coccobacilli. Common rickettsial diseases are Q fever, Rocky Mountain spotted fever, Mediterranean spotted fever, epidemic and murine typhus, and acute febrile cerebrovasculitis. Most of these conditions cause systemic angiitis with microvascular damage of multiple organs, including the nervous system. Rickettsial angiitis is related to the proliferation of microorganisms within endothelial cells causing endothelial swelling and necrosis, increased vascular permeability, recruitment of mononuclear inflammatory cells, liberation of procoagulant factors, and formation of microthrombi with luminal occlusion.

The clinical picture of rickettsial diseases is more or less homogeneous. Initial manifestations include fever, myalgias, headache, and a macular rash. Neurological manifestations appear after a few days and include behavioral changes, seizures, loss of consciousness, and various combinations of focal signs (Marrie and Raoult, 1992; Bleck, 1999). Cerebrospinal fluid analysis usually shows a mild mononuclear pleocytosis and increased protein content. Neuroimaging studies may be normal or may show diffuse brain swelling. Well-defined cerebral infarctions have been reported in some patients. Ischemic lesions are most often located in the subcortical white matter of cerebral hemispheres (Bonawitz et al., 1997). Diagnosis of rickettsial diseases rests on the demonstration of specific immunofluorescent antibodies in biopsy specimens. Therapy includes tetracyclines or chloramphenicol, and the prognosis depends on the specific disease and the neurological status of the patient on admission.

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Chapter 44

Vasculitis and stroke

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44.1. Introduction

A common perception is that the typical clinical picture seen in large-vessel cerebral stroke is rarely caused by vasculitis, but that its "treatability" more than counterbalances its rarity in justifying its consideration in the differential diagnosis of large-vessel stroke, and likewise in any comprehensive account of stroke. This rationale is essentially incorrect, but cerebral vasculitis nonetheless properly belongs in any such account, for entirely separate reasons.

The widespread anxiety among physicians and neurologists that a patient presenting with a classic picture of large-vessel "stroke"—an abrupt-onset hemiparesis, say, in an otherwise well individual—that might be caused by vasculitis, particularly isolated CNS vasculitis, feared because of the defining absence of systemic clues, is almost entirely misplaced. Such a presentation is in truth vanishingly rare. Why has this near-mythical picture emerged? First, a significant proportion of reported cases of "stroke caused by CNS vasculitis" do not have pathological confirmation and are very likely to have other disorders or vasculitis outside the CNS. Some of the much-cited series listing stroke as a typical clinical feature of cerebral vasculitis have included patients with lymphoma or other malignancies, Herpes zoster (see later in this chapter), sarcoid, and/or giant cell arteritis (Younger et al., 1988). Others allow the diagnosis to be based on contrast angiography alone (Calabrese and Mallek, 1988). The great majority of individuals described as having "stroke from *lupus cerebral vasculitis*" have lupus but not vasculitis; likewise most CNS vasculopathies due to cocaine and other drugs of abuse are not vasculitic.

Of the remaining pathologically-confirmed cases, as Schmidley (2000) has pointed out in his excellent monograph, the clinical picture is hardly that of a classic stroke: there is often "preceding or concomitant evidence of more widespread CNS disease," with features which immediately would point away from a conventional atherosclerotic or embolic stroke (commonly preceding *progressive* neurological features, malaise, weight loss, fever, etc.).

Primary *large-vessel* vasculitides can present with a neurological picture more closely resembling classic stroke, including temporal arteritis and Takayasu's disease (Pego-Reigosa et al., 2004). Here though, technically the vasculitic process rarely involves the intracranial circulation, and in any case the clinical context and other features do not permit serious diagnostic confusion with the conventional atheromatous thrombo-embolic CVA; it is rather the medium and small-vessel CNS vasculitis that is feared by the physician.

In these disorders, the affected vessels are less than 0.5 mm in diameter (Hankey, 1991), though others have suggested 100–200 μm (Kendall, 1984). Not only does this help to explain the difficulties of interpreting contrast angiography in pursuing a diagnosis of this disorder (vide infra), it also begins to explain why large-vessel occlusion is not a direct feature of most forms of cerebral vasculitis, and why the related clinical picture of "stroke" is profoundly uncommon.

Isolated CNS vasculitis could, in principle, cause this presentation since large-vessel disease—occlusion, aneurysm, and/or hemorrhage—may occur as a secondary consequence of vasculitic changes in *vasa vasora*, leading to damage to the larger vessels they perfuse. In practice, intracerebral hemorrhage (ICH) may be the least uncommon, 14 of 68 patients with pathologically confirmed CNS vasculitis having had ICH at some point in their course in Schmidley's

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series (2000) (though in at least one such case, amyloid angiopathy-related cerebral vasculitis [Scolding et al., 2005] rather than idiopathic disease may have been present). Ferro, looking specifically at young age groups where vasculitis would be expected to be disproportionately highly represented, described only 1 case among 515 consecutive patients with ICH, and 8 out of 254 (3%) stroke patients aged under 50 years (Ferro, 1998). Significantly, even here there was no histopathological confirmation, the original report listing these 8 patients as having "non-atherosclerotic cerebral vasculopathy" (Ferro and Crespo, 1988), which could of course include lupus, cocaine, and so on.

In summary, "stroke" rarely occurs as a result of cerebral vasculitis, and when it does, the clinical features and context almost invariably point towards inflammatory disease and away from more common causes of stroke in the overwhelming majority of, and possibly all, cases (see Table 44.1). However, the pathological changes in CNS vasculitis indicate why, regardless of this frequency, vasculitis should be considered herein. As described in more detail below, the principal consequence of the destructive inflammatory change within the vessel wall is, commonly, vascular occlusion. This is the key pathophysiological change. Microvascular occlusion and subsequent local ischemia and infarction are the main causes of neurological disturbance in cerebral vasculitis, just as they are in large(r) vessel stroke; this is why vasculitis must be included in coverage of "stroke."

44.2. Large-vessel arteritis

There are two primary large-vessel vasculitic diseases which, while not strictly CNS vasculitides, can involve the CNS: Takayasu's arteritis and giant cell or temporal arteritis. They present few of the complexities of "true" CNS vasculitis and, also by way of contrast, readily cause large-vessel stroke. By way of introduction, these will be considered first.

Table 44.1

True vasculitis as a cause of stroke is not just uncommon, but rare

Clinical setting leading to labeling "vasculitis"	True underlying pathology
Lupus/antiphospholipid syndrome	Non-inflammatory microthrombotic vasculopathy
Cocaine etc.	Vascular spasm
Herpes zoster infection	May be true (reactive) vasculitis
Stroke-like picture with "vasculitis" diagnosed on angiography	See Table 44.3 for causes of angiographic changes
Stroke with jaw claudication, polymyalgia rheumatica, raised ESR, etc., and/or limb ischemia	Large-vessel vasculitis—GCA, Takayasu's arteritis

44.2.1. Takayasu's arteritis

Alternatively named "pulseless disease," this is a rare disorder which only rarely causes stroke. Strictly speaking, it is not a CNS vasculitis: it affects the aortic arch and its main branches, but rarely extends to the smaller-vessel intracranial circulation. Nonetheless it may cause stroke, either directly through carotid or vertebrobasilar involvement, or indirectly through cardiac disease and embolism, or renal artery involvement and hypertension. Hypertensive encephalopathy can also occur.

Takayasu's disease was originally described in young oriental women, and although uncommon outside this group, is now globally recognized, as a recent excellent Italian study demonstrates (Vanoli et al., 2005). Characteristic involvement of the aorta and its large branches results in the vast majority of affected individuals—some 98%—having at least one major arterial pulse absent. The disease process is initially one of granulomatous inflammatory (and later occlusive) change, during which phase most of the neurological abnormalities occur. Syncope is reported in at least 50% of patients, but also seen are strokes, transient ischemic attacks, and visual abnormalities—all exacerbated by hypertension. In addition to the limb vasculature, any of the four main arteries supplying the brain can be involved. A typical presentation would therefore be one of limb claudication, with one or more absent pulses, a systolic blood pressure difference between the arms of >10 mmHg, and the presence of arterial bruits, in a patient under the age of 40 years. This may follow a phase of systemic symptoms, with malaise, fever, weight loss and arthralgia, and a raised erythrocyte sedimentation rate (ESR). Early histological features of the disease include granulomatous changes in the media and adventitia of the aorta and its branches, later followed by intimal hyperplasia, medial degeneration, and sclerotic adventitial fibrosis.

There have been no controlled clinical therapeutic trials, and in a proportion of patients the disease appears to be self-limiting and monophasic. However, steroids are commonly used for treatment. Approximately 50% of patients also require further immunosuppressant therapy (Vanoli et al., 2005), and there is uncontrolled evidence for the combination of steroids and azathioprine (Valsakumar et al., 2003). The ESR has been reported to be of little value in monitoring progress (Kerr et al., 1994).

44.2.2. Temporal arteritis

Temporal arteritis involves large and medium-sized arteries. Like Takayasu's disease, temporal arteritis is principally a disorder of extracranial vessels, the inflammatory process rarely extending beyond the point of penetration of the dura. Unlike Takayasu's, however, the external and internal carotid arteries are not commonly involved, while the superficial temporal, posterior ciliary, and ophthalmic arteries are targeted. Vertebral artery involvement and brainstem ischemia are more common, possibly since the posterior cerebellar artery retains an internal elastic lamina (Wilkinson and Russell, 1972; Caselli and Hunder, 1994). Temporal arteritis rarely affects individuals less than 55 years of age, and affects women twice as commonly as men. It is far from rare, with an overall prevalence of 100–150/10^5 (Huston et al., 1978) and an incidence in the over-50s of 17.4/100,000/year.

Classically it manifests as uni- or bilateral scalp pain, often severe, with exquisite tenderness and accompanying tender, pulseless, nodular temporal arteries. Symptoms of general malaise, jaw claudication and features of polymyalgia rheumatica—stiffness and aching of the shoulder girdle, worse in the mornings—often only emerge on direct enquiry. Such symptoms, with a raised ESR (and often a normochromic normocytic anemia) should lead to urgent steroid treatment (see below) and a tolerably urgent temporal artery biopsy. Diagnostic changes may still be apparent in biopsies taken 2 or even 4 weeks after the commencement of steroids (Achkar et al., 1994; Ray-Chaudhuri et al., 2002). A specimen of several centimeters length is recommended to help avoid false-negative results, which can otherwise result from the focal or multifocal nature of the disorder (Fernandez, 1988; Kent and Thomas, 1990).

Histopathological examination reveals vasculitis, with an inflammatory infiltrate comprising mononuclear and multinucleated giant cells; the latter phagocytose the elastic laminae, causing characteristic fragmentation (Parker et al., 1975). Acutely, granulomata may be present. Fragmentation of the elastic laminae is an important diagnostic feature which persists after inflammatory changes have subsided.

A proposed sequence of events is that $CD4^+$ T cells are first activated within the adventitia following interaction with local dendritic cells. IFN-gamma-producing $CD4^+$ T cells orchestrate macrophage differentiation and, together with activated macrophages, contribute to granuloma formation. Macrophages also secrete growth factors, which trigger local arterial intimal hyperplasia and thence vascular occlusion (Weyand et al., 2004; Ma-Krupa et al., 2005). Immunoglobulin and complement deposits are apparent in lesions (Liang et al., 1974).

Neuro-ophthalmological symptoms are the most widely recognized and feared. Blindness occurs as a consequence of anterior ischemic optic neuropathy following vasculitic involvement of the posterior ciliary arteries and/or the parent ophthalmic artery; it is seen in one-sixth of treated patients with the condition (Caselli and Hunder, 1994). Central retinal artery occlusion is much less common (Mehler and Rabinowich, 1988). The typical picture comprises (locally) painless loss of acuity, commonly severe, often with an altitudinal field defect. The fundal appearances may be normal, although swelling (usually mild) may be seen. Visual loss, regardless of treatment, rarely subsequently reverses (nesh-Meyer et al., 2005); loss of vision in one eye, perhaps not surprisingly, indicates an extremely high risk of imminent loss in the other.

Intracranial involvement is not common. Although one study of 166 patients with biopsy-proven disease suggests neurological involvement in 31%, including neuropsychiatric syndromes, peripheral neuropathies, spinal cord lesions, neuro-otological syndromes, various pain syndromes, transient ischemic attacks and stroke, most authorities would find almost all these pictures well outside their common experience (Caselli and Hunder, 1994). Stroke or TIA may be seen in approximately 7% of patients (Caselli et al., 1988), infarction of the vertebrobasilar territory is considered relatively common, and embolic episodes can also occur (Wilkinson and Russell, 1972).

44.2.3. Treatment

Oral steroids, urgently exhibited, remain the treatment of choice. High doses (60–80 mg per day) are generally recommended (Myles et al., 1992), with some suggesting the initial use of higher-dose intravenous methylprednisolone (1 g daily for 3 days) in those with compromised vision. Clinical enthusiasm for lower doses of steroids, despite some evidence that they are equally efficacious (Mason and Walport, 1992; Nesher et al., 1997), has been limited.

Steroids may be reduced slowly—perhaps in 5 mg decrements weekly—after 1 week (some would say 4 days, particularly if a higher starting dose is used), to a maintenance dose of perhaps 10 mg daily. Thereafter, some would suggest continuing for periods of 12–24 months before a complete (closely monitored and phased) withdrawal; others suggest a slow (1 mg decrements/month), continued reduction (Mason and Walport, 1992). Cessation of steroids after 6 months' symptom free treatment on only 2.5 mg daily has been

suggested (Nordborg et al., 1995). Temporal arteritis is generally a self-limiting condition lasting 1–2 years, although some patients appear still to require steroids 2–5 years on (Kyle and Hazelman, 1990).

The ESR is commonly used to monitor treatment response (Kyle et al., 1989). However, a low ESR in active disease may not be excessively rare, perhaps explained by an inability to mount an acute phase response, or by very localized arteritis (Salvarani and Hunder, 2001). Recent work has also emphasized that an elevated platelet count should be considered a risk factor for permanent visual loss in temporal arteritis and should accentuate the need for urgent treatment (Lincoff et al., 2000). The treatable or preventable long-term consequences of corticosteroids (Nesher et al., 1994) should not be overlooked. Steroid resistance is extremely rare. Azathioprine is often used as a steroid-sparing agent, rather than a "second-line" agent (De Silva and Hazleman, 1986); perhaps surprisingly, methotrexate does not appear useful (Hoffman et al., 2002).

4.3. Medium- or small-vessel CNS vasculitis

Vasculitis is a pathological picture more than a disease or a diagnosis. The changes include, by definition, blood vessel inflammation with additional, specific, and defining pathological features, together producing different but frequently overlapping clinical manifestations (Watts and Scott, 1997). The classic core histopathological change consists of an inflammatory infiltrate within (not just around) the vessel wall, associated with destructive mural changes ("fibrinoid necrosis"), precipitating vascular occlusion and therefore infarction and ischemia. The further histological characteristics, which allow disease-specific classification, include the presence or absence of granulomata, of eosinophils, and/or the size of the vessel implicated (Table 44.2).

The clinical and histopathological picture of CNS vasculitis can occur in three contexts. First, primary or idiopathic isolated CNS vasculitis can occur, wherein disease is wholly confined to the nervous system (though in fact more detailed autopsy studies show that systemic vasculitic change can be seen in various organs [Lie, 1997b]). Second, there are a number of primary systemic vasculitides, usually involving the lungs and/or kidneys—for example, polyarteritis and Wegener's granulomatosis—which can also secondarily affect the nervous system. Third, systemic rheumatological or connective tissue diseases can number vasculitis among their complications, even though this is not their primary or common underlying pathology. When this does occur, CNS involvement can be seen. Finally, other factors extraneous (to the brain) can also trigger vasculitis (drugs, infections, etc.). All will be briefly considered.

44.3.1. The clinical features of medium/small-vessel CNS vasculitis

There is no typical clinical picture of CNS vasculitis. Focal or multifocal infarction or diffuse ischemia affecting any part of the brain and occurring as an isolated event, recurrently, or progressively, underlie the protean manifestations and a wide variation in disease activity, course, and severity. Therefore a mixture, in unpredictable proportions, of headaches (40–50%), focal or generalized seizures (10–20% [Schmidley, 2000]), stroke-like episodes with hemispheric or brainstem deficits, acute or subacute encephalopathy, progressive cognitive changes, chorea, myoclonus and other movement disorders, and optic and other cranial neuropathies, can all occur. The course is commonly acute or subacute, but chronic progressive presentations are also well-described, as are spontaneous

Table 44.2

Classification of the vasculitides according to size

Dominant vessel involved	Primary	Secondary
Large arteries	Giant cell arteritis Takayasu's arteritis	Aortitis with rheumatoid disease; infection (e.g., syphilis)
Medium arteries	Classic polyarteritis nodosa Kawasaki's disease	Infection (e.g., hepatitis B)
Small vessels and medium arteries	Wegener's granulomatosis Churg–Strauss syndrome Microscopic polyangiitis	Vasculitis with rheumatoid disease, SLE, Sjögren's syndrome, drugs, infection (e.g., HIV)
Small vessels	Henoch–Schönlein purpura Essential cryoglobulinemia Cutaneous leukocytoclastic vasculitis	Drugs (e.g., sulphonamides, etc.) Infection (e.g., hepatitis C)

relapses and remissions. Systemic features such as fever (10% (Schmidley, 2000)), night sweats, livedo reticulares or other skin rashes, or oligoarthropathy may also be present (importantly from a diagnostic perspective, these are usually revealed to the physician only on direct questioning).

The analyses of the largest number of patients with *histopathologically confirmed* CNS vasculitis are those of Hankey (1991), and that published by Schmidley in his extremely valuable and authoritative monograph (2000). Herein of course lies a paradox: the poor sensitivity and specificity of contrast angiography and indeed every other test for CNS vasculitis tell us that any series not restricted to histopathologically confirmed cases is highly likely to be contaminated by other diseases. But if only cases subject to autopsy or biopsy are to be included, then it is surely inevitable that only cases at the more severe end of the spectrum will be included. Hankey's figures—for example, stupor or coma being seen in 42% of patients in whom the diagnosis was confirmed at autopsy, compared to 15% of those where biopsy was the means of diagnosis (Hankey, 1991)—offer objective support for this "tissue confirmation effect." The present author believes there is no answer to this.

Notwithstanding this reservation, the same range of features emerged but, valuably, an analysis of the proportions falling into various clinical presentations was offered. Thus an acute presentation occurred in 11 of 68 patients, subacute in 21, and chronic in 38 (Schmidley, 2000). In 29 cases focal features were apparent at presentation, in 15 multi-focal, and in 30 diffuse or non-localizing.

Such diversity helps to explain the difficulty of diagnosis—recognizing even the possibility of neurological vasculitis is often not straightforward. To attempt to address this difficulty, three broad categories (emphatically not intended to imply either pathological or therapeutic differences) have been defined (Scolding et al., 1997). These may help to improve recognition of the condition.

1. Acute or subacute encephalopathy, commonly presenting as an unremarkable acute confusional state, progressing to drowsiness and coma.
2. A picture superficially or even rather closely *resembling* atypical multiple sclerosis ("MS-plus") in phenotype—with perhaps a relapsing–remitting course, and features such as optic neuropathy and brainstem episodes—but also accompanied by other features less common in multiple sclerosis such as seizures, severe, and persisting headaches, encephalopathic episodes, or hemispheric stroke-like episodes;
3. Presentation with an intracranial mass lesion, with headache, drowsiness, focal signs and often elevated intracranial pressure.

Stroke-like events as an isolated presentation did not feature as a separate category in our analysis because we observed no patients with isolated (large-vessel) stroke in our series. It should be emphasized that these three pictures are not exclusive, and repeated that we have no reason to believe that CNS vasculitis presenting in one or other fashion carries different etiological, pathological, or prognostic implications. This list is aimed merely at raising awareness of the possibility of vasculitis, when appropriate, in the neurological differential diagnosis.

44.4. Investigation of suspected CNS vasculitis

The first stage of diagnosis is thinking of the disorder. Many diseases may also of course cause clinical patterns such as those above (see also Table 44.3). The diagnosis of cerebral vasculitis therefore has three further stages: exclusion of alternative possibilities, confirmation of intracranial vasculitis, and pursuit of the cause of the vasculitic process (Joseph and Scolding, 2002). No single

Table 44.3

The differential diagnosis of cerebral vasculitis

Other vasculopathies	*Infections*
Susac's syndrome	Lyme disease
Homocysteinuria	AIDS
Ehlers–Danlos syndrome	Endocarditis
Radiation vasculopathy	Whipple's disease
Köhlmeyer–Degos disease	Viral encephalitis
Fibromuscular dysplasia	Legionella/mycoplasma pneumonia
Fabry's disease	*Tumors and malignancy*
Moyamoya disease	Atrial myxoma
Amyloid angiopathy	Multifocal glioma
CADASIL*	Cerebral lymphoma
Marfan's syndrome	Paraneoplastic disease
Pseudoxanthoma elasticum	Multiple cholesterol emboli
Viral or fungal vasculitis	Hypertension (severe)
Other immune/inflammatory diseases	Eclampsia
Sarcoidosis	Thrombotic thrombocytopenic purpura
Lupus and anti-phospholipid disease	Cerebral sinus thrombosis
Behçet's syndrome	Mitochondrial disease
Multiple sclerosis/ADEM	Migraine
Thyroid encephalopathy	

simple investigation can confirm a diagnosis of cerebral vasculitis but some can exclude it.

44.4.1. Laboratory tests

In patients where there is a strong suspicion of cerebral vasculitis, it is important to recognize that the principal function of all investigations is not to prove intracranial vasculitis but to exclude alternative possibilities or assess other organ involvement. The only test for which this is not true is cerebral biopsy, for which both these outcome alternatives are equally important. CSF and blood tests and radiological investigations alike can raise or sustain the likelihood of, but by no means confirm, CNS vasculitis.

Thus, the leukocytosis or anemia present in about 50% of patients, and commonly abnormal ESR and C-reactive protein levels, are entirely non-specific. Some include a normal ESR as a defining feature of isolated CNS angiitis; we found moderately elevated values in two-thirds of patients (Scolding et al. 1997); Schmidley in his series cites 47% having a normal ESR (< 20), though in only 9% was the measure over 60 (Schmidley, 2000). Serological testing antinuclear antibody (ANA), antineutrophil cytoplasmic antibody (ANCA) etc. is vital to exclude lupus and/or help define any systemic origin of an established intracranial vasculitis. "False" ANCA positivity is sometimes seen in connective tissue disorders such as lupus and rarely in individuals with no apparent vasculitic disorder at all.

CSF analysis may suggest inflammation within the CNS, and/or help exclude infective or malignant diseases. Increased red cell numbers may suggest hemorrhage. Pooled case reviews suggest an elevation in cell count (mainly a lymphocytosis) and/or protein in 50–80% (Calabrese and Mallek, 1988; Hankey, 1991; Scolding, 1999a; Schmidley, 2000). The CSF opening pressure is raised in almost 50% of primary angiitis of the CNS (PACNS) cases. Schmidley reports a raised glucose level (72% patients) as an additionally useful pointer, but cites entirely normal contents in 9% (Schmidley, 2000). Oligoclonal immunoglobulin bands in the CSF have been studied infrequently, but are found occasionally (perhaps up to 40–50% [Scolding et al., 1997]) sufficient to render analysis worthwhile. Oligoclonal band patterns which vary substantially, perhaps even disappearing altogether during the course of disease, do help point away from multiple sclerosis should this form part of the differential diagnosis.

44.4.2. Radiology

CT is normal in up to two-thirds of cases (Schmidley, 2000). Magnetic resonance imaging (MRI) is sensitive but not specific (Harris et al., 1994), disclosing the results of vascular inflammation, not vasculitis itself. Ischemic areas, periventricular white matter lesions, hemorrhagic lesions, and parenchymal or meningeal enhancing areas can be seen. Correlation between MR changes and blood vessel involvement may be poor; in one study, of 50 territories affected by vasculitis on contrast angiography, at least one-third were normal on MRI (Cloft et al., 1999). Other studies confirm this imperfect sensitivity, and there are (unfortunately) reported cases of proven cerebral vasculitis with normal MR imaging.

SPECT appears to be a useful but non-specific imaging tool, again reflecting but not defining a vasculitic process (Scolding et al., 1997). The value of PET scanning in this context has yet to be clarified.

Magnetic resonance angiography (MRA) is finding a niche in imaging of large-vessel vasculitides such as Takayasu's arteritis and classic polyarteritis nodosa, with potential to supplant contrast angiography (Atalay and Bluemke, 2001), but does not enjoy sufficient resolution to help in medium- or small-vessel cranial vasculitis.

Establishing the diagnostic value of contrast angiography is complicated by the many studies which have used this as the "gold standard" for confirmation. Publications that have pathological evidence indicate a false-negative rate for angiography of 30–40% (Calabrese and Mallek, 1988; Hankey, 1991; Schmidley, 2000), and there have been examples of patients with histologically proven PACNS who have completely normal angiograms. This may be explained by the affected vessels being beyond the resolution of conventional imaging. When abnormalities are present, they include segmental (often multifocal) narrowing with areas of localized dilatation or beading. Single stenotic areas in multiple vessels are more frequent than multiple stenotic areas along a single vessel segment in PACNS. An enormous number of inflammatory, metabolic, malignant, or other vasculopathies can mimic angiitis (Table 44.3). Some authorities have reported a contrast angiography risk of transient (10%) or permanent neurological deficit (1%) (Hellmann et al., 1992), but most currently would put the figure significantly lower.

Contrast angiography is a valuable investigational tool *as long as it is not over-interpreted*. It may offer a contribution towards building (or dismantling) the case for CNS vasculitis, or of course point towards alternative, otherwise non-diagnosable vasculopathies (radiation vasculitis, moyamoya, or fibromuscular dysplasia, for example). Indium-labeled white cell nuclear scanning has a limited role, particularly in disclosing areas of (sometimes unsuspected) systemic inflammation (Scolding et al., 1997).

44.4.3. Ophthalmological examination

Careful ocular examination, including slit lamp study, is important—again, not least as a means of disclosing asymptomatic conjunctival, anterior or posterior, or retinal (and thence probable neurological) sarcoidosis, Behçet's disease, or other inflammatory disorders. Where available, dynamic recording of erythrocyte flow using video slit lamp microscopic recording and low-dose fluorescein angiography to examine the vasculature of the anterior ocular chamber can be a useful additional investigation (Scolding et al., 1997).

44.4.4. Histopathological diagnosis

Histopathological confirmation, by biopsy of an abnormal area of brain where possible, or by "blind" biopsy, incorporating meninges and non-dominant temporal white and gray matter, is the only way of procuring a definite diagnosis in patients with idiopathic CNS vasculitis. Biopsy may alternatively reveal an underlying process not otherwise suspected, often with profound therapeutic implications, such as infective or neoplastic (principally lymphomatous) vasculopathies. Biopsy is, of course, hardly a trivial procedure, carrying a risk of serious morbidity estimated at 0.5–2% (though more recent estimates are significantly lower [Alrawi et al., 1999]). Sensitivity is also limited to (at best) approximately 70% (Calabrese and Mallek, 1988; Hankey, 1991; Alrawi et al., 1999). However, it is reported that up to 75% of reported cases may be "diagnosed" without histopathology (Lie, 1997b). The non-specific nature of other investigations, particularly angiography, the severity of the disease in question, the hazards of proper treatment if misapplied, and the potential treatability of alternative conditions which may mimic CNS vasculitis create a strong case for pursuing a tissue diagnosis whenever possible (Joseph and Scolding, 2002).

A recent retrospective study of some 61 patients biopsied for suspected cerebral vasculitis showed no patients suffering any significant morbidity as a result of the procedure (Alrawi et al., 1999). Thirty-six percent of patients were confirmed as having cerebral vasculitis but, no less usefully and importantly, 39% biopsies showed an alternative, unsuspected diagnosis—lymphoma (six cases), multiple sclerosis (two cases), or infection (seven cases, including toxoplasmosis, herpes, and also two cases of cerebral abscess). Many of these non-vasculitic disorders are treatable (and often curable), while inappropriate treatment with steroids alone, or with more potent immunosuppressive agents, would at best have no useful effect, and very often serious adverse consequences. Biopsy failed to yield a clear diagnosis in 25% of patients in this study, though even here, biopsy might not be described as "non-contributory": it has at least helped reduce the possibility of the alternative diagnoses mentioned above. The decision not to biopsy must be balanced against the harmful effects of immunosuppressive drugs used potentially unnecessarily. When vasculitis is seen at cerebral biopsy, specific and defining characteristics of the causative disease process may also be apparent; if not, these must now be painstakingly sought.

44.5. The defining features of specific vasculitides

44.5.1. Primary (isolated) angiitis of the nervous system

Primary CNS vasculitis is a focal and segmental angiitic process, and may be granulomatous, necrotizing, or lymphocytic in character, often with mixed morphologic types in individual patients (therefore rendering the common title of "granulomatous angiitis" difficult to sustain). Vasculitis is confined to the brain and/or spinal cord; it is in essence defined by the absence of systemic vasculitic or indeed other disease, and cannot safely be diagnosed without tissue biopsy. The relationship to other primary (systemic) vasculitides is not simple, however. Many of these disorders (see below) also show marked organ predilection, and the "exclusiveness" of primary CNS vasculitis to the nervous system is not perfect; autopsies not uncommonly reveal subclinical extracranial involvement. These may contribute to the more systemic features such as fever, rigors, weight loss, raised plasma viscosity, and so on.

Two unusual, eponymous, non-systemic primary disorders may involve the CNS. Cogan's syndrome mostly affects young adults, and is characterized by recurrent episodes of interstitial keratitis and/or scleritis with vestibulo-auditory symptoms, which may be complicated by CNS, PNS, or systemic vasculitis (Vollertsen, 1990). In Eale's disease, an isolated retinal vasculitis occurs, causing visual loss; again, neurological complications are well-described (Dastur and Singhal, 1976; Singhal and Dastur, 1976).

44.5.2. Primary systemic vasculitides with neurological involvement

The systemic vasculitides carry their own defining clinical and laboratory characteristics. Most may be complicated by neurological involvement, although in general the peripheral nerves appear more susceptible

than the CNS. Constitutional disturbances—fever, night sweats, severe malaise, and weight loss—are common and may be accompanied by a rash or arthropathy.

Polyarteritis nodosa has perhaps been the longest recognized—although now is generally subdivided into classic (macroscopic) polyarteritis nodosa and microscopic polyarteritis nodosa (Jennette et al., 1994a; Guillevin and Lhote, 1995). This distinction is not, however, universally accepted (see Lie, 1994, for a critique).

Classic polyarteritis nodosa mainly affects medium-sized vessels, and is an unusual disorder. Multiple organ involvement is common, though 80% of patients present with renal failure and hypertension. Gastrointestinal involvement occurs in up to 50%, with abdominal pain due to visceral infarcts. Heart failure and myocardial infarction reflect cardiac involvement. Neurological abnormalities are prominent, but mostly confined to the peripheral nervous system—up to 70% of patients have a peripheral neuropathy (Guillevin et al., 1992). It is thought that damage is initiated by immune complex deposition; fibrinoid necrosis is typical though not diagnostic. Although there are no specific serological tests, about 20–30% have hepatitis B antigen or antibody in serum. ANCA serology is usually negative (Guillevin et al., 1993), and the diagnosis is commonly based on visceral angiography, which shows aneurysms or occlusions of the renal or mesenteric arteries (Fig. 44.1).

Microscopic polyangiitis is a small-vessel vasculitis, and is usually pANCA positive. Renal disease is almost invariable, but multisystem involvement common. Microscopic polyarteritis nodosa can resemble Wegener's granulomatosis, but granuloma formation is not seen and upper respiratory tract involvement is rare. Mononeuritis multiplex has been recorded in 55% of patients (Guillevin et al., 1999), but CNS involvement is much less common (in this study, some 11%).

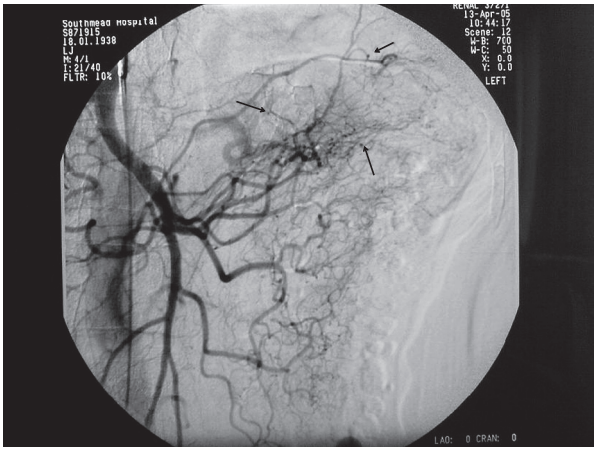

Fig. 44.1. Mesenteric angiogram of a patient with polyarteritis showing multiple small aneurysms (arrowed).

Wegener's granulomatosis was relatively later delineated (see Fauci and Wolff, 1973, for example). It differs from microscopic polyarteritis nodosa in predominantly affecting the respiratory tract, both upper and lower (the nose, often with destructive cartilaginous changes causing the characteristic saddle nose deformity, the sinuses, larynx, trachea and lungs), and in being cANCA positive, with proteinase-3 specificity. This histopathology also differs, with a necrotizing, granulomatous vasculitis. Renal disease occurs in 80% of patients. Neurological involvement is seen in up to 35% of patients (Nishino et al., 1993), but most commonly targets the peripheral nervous system.

However, CNS disease can occur through a variety of mechanisms. First, cerebral small-vessel vasculitis may rarely be seen, causing features clinically indistinguishable from any other form of intracranial vasculitis (Nishino et al., 1993). Second, and (significantly) specific to Wegener's disease, direct effects of the granulomatous process can involve the CNS. Contiguous invasive spread from Wegener's affecting the upper respiratory tract or sinuses can cause granulomatous meningitis, and with this a variety of cranial neuropathies (approximately 6% of patients) (Nishino et al., 1993). The seventh and eighth nerves are particularly susceptible to involvement from middle ear disease. Gadolinium-enhanced MR scanning may valuably reveal meningeal thickening and infiltration, offering a ready target for biopsy. Ocular involvement may occur with orbital pseudotumors reported in 5% of 324 patients with Wegener's granulomatosis. Additionally, CNS disease remote from the respiratory tract can occur through metastasis of granulomata from the primary site.

Churg–Strauss syndrome is the last delineated vasculitic disorder (so far!). It is also a multisystem disease, but is characterized clinically by prominent asthma with an eosinophilia. About 50% of patients are positive for pANCA, 25% positive for cANCA, and 25% have no antineutrophil cytoplasmic antibodies. Pathologically, a granulomatous necrotizing vasculitis is apparent. Skin involvement, with purpura, urticaria, and subcutaneous nodules, is common and glomerulonephritis may develop. Churg–Strauss syndrome may also affect coronary, splanchnic, and cerebral circulations. Peripheral neuropathy is common, particularly mononeuritis multiplex, but CNS involvement is evident in only about 7% (Sehgal et al., 1995).

Henoch–Schönlein purpura mainly affects children, affecting the skin, gastrointestinal tract, joints and

kidneys. Cerebral vasculitis is reported as a complication but without tissue proof of the process. Kawasaki's disease, or mucocutaneous lymph node syndrome, also mainly affects children. Commonly it presents as an acute febrile illness with conjunctival injection, dryness of the lips with a strawberry tongue, cervical lymphadenopathy, a polymorphic rash, and a hand–foot syndrome. Acutely, a pan-carditis and a coronary arteritis may complicate the illness; coronary artery aneurysm represents a longer-term complication. Neurologically, aseptic meningitis, encephalopathy and facial palsy are reported. Hemiplegic strokes are also described, possibly embolic. Pathologically, an acute systemic inflammatory vasculitis, with little or no fibrinoid necrosis, underlies the disease. Kawasaki's disease is one of the very rare vasculitic illnesses enjoying class I evidence for treatment with intravenous immunoglobulin.

44.6. CNS vasculitis as a complication of "non-vasculitic" systemic disorders

44.6.1. Autoimmune and connective tissue disease

Neurological or psychiatric symptoms in systemic lupus erythematosus are common (40–50%) (Scolding and Joseph, 2002), but the most frequent neuropathological finding is not vasculitis but a non-inflammatory vasculopathy of small arterioles and capillaries, with resulting microinfarcts and microhemorrhages. Histopathological studies have consistently demonstrated that, while vasculitis of the cerebral vessels can occur, it is rare, with an incidence of 7–13%. Serology naturally forms the mainstay of diagnosis.

Sarcoidosis affects the nervous system in only 5% of cases, commonly presenting with optic and/or other cranial neuropathies (especially involving the facial nerve) usually due to granulomatous meningeal and brainstem infiltration. Sarcoidosis may be complicated by systemic vasculitis affecting small or large caliber vessels in a similar fashion to other vasculitides, with angiographic and indeed histological evidence of CNS vasculitis. Serum angiotensin converting enzyme (ACE) and calcium levels are not always raised. Cerebrospinal fluid abnormalities are seen in 80%, usually with an elevated protein and pleocytosis, and oligoclonal bands are positive in about 45%. Cranial MRI shows non-specific multiple white matter lesions or meningeal enhancement; whole body gallium scanning can be more useful, demonstrating a characteristic pattern of uptake (particularly affecting the parotid glands and lungs). Pathological diagnosis by the Kveim test is now rather rarely performed. Biopsy of cerebral or meningeal tissue provides the most reliable basis for treatment (Zajicek et al., 1999).

Seropositive rheumatoid disease is a well-recognized precipitant of cerebral vasculitis (Scolding, 1999b), though skin involvement and mononeuritis multiplex are far more typical manifestations of rheumatoid vasculitis. There are unusual reports of CNS angiitis in the context of systemic sclerosis, Sjögren's syndrome and mixed connective tissue disease, even (though rarely) without a preceding history of systemic symptoms.

44.6.2. Infections

Infection-related vasculitis (Lie, 1996) occurs through direct invasion of the vessel wall (aspergillus, histoplasma, coccidioides), immune complex deposition (hepatitis B, Epstein–Barr virus, cytomegalovirus (CMV), Lyme disease, syphilis, and malaria), and/or secondary cryoglobulinemia (hepatitis B and C, Epstein–Barr virus, CMV Lyme disease, syphilis, malaria, and coccidiomycosis all have been linked to mixed cryoglobulinemia). In HIV infection, CMV and toxoplasma may precipitate vasculitis, and syphilitic cerebral vasculitis has re-emerged in this context. Bacterial causes of meningoencephalitis—mycobacteria, pneumococci and *H. influenzae*—may also trigger intracranial vasculitis.

Herpes zoster ophthalmicus warrants particular attention. This infection can cause secondary, localized CNS vasculitis within the ipsilateral hemisphere, probably by direct viral invasion of blood vessels (Hilt et al., 1983), producing single or multiple smooth-tapered segmental narrowing on angiography. The characteristic clinical picture, seen in approximately 0.5% of cases, is that of an acute monophasic hemiparesis contralateral to the (usually by now resolving) ocular disease. The latent period may last from days to months, but is usually of the order of 3–4 weeks. A cerebrospinal fluid mononuclear pleocytosis and raised varicella-zoster antibody titer help in the diagnosis. A more generalized necrotizing and granulomatous vasculitis can also occur, although the picture here is complicated by a number of cases where pathological vascular changes other than those of vasculitis were described—or where the diagnosis was based only on angiographic abnormalities. Complications of shingles may affect children similarly, though there have been less frequent reports of chickenpox triggering cerebral vasculitis. Occasionally only the spinal cord is involved in herpetic disease; rarely, more generalized vasculitis may occur with ophthalmic or remote zoster infection.

Chronic viral infection with parvovirus B19 has been implicated in polyarteritis nodosa, Kawasaki disease, and Wegener's granulomatosis, though causality is by no means proven (Lie, 1996). Tuberculosis-

associated vasculitis may be driven by tuberculoprotein immune complexes. Hepatitis B, Epstein–Barr virus, CMV, Lyme disease, syphilis, and malaria cause vasculitis by a similar mechanism, while in coccidiomycosis, vascular inflammation is either direct or via cryoglobulinemia.

In southwestern USA and Northern Mexico, spores of the *Coccidioides immitis* fungus may be inhaled. Subsequent hematogenous spread to the meninges can occur. Vasculitis involving the small penetrating branches of the major cerebral vessels, and consequent deep ischemic infarction—or, rarely, subarachnoid hemorrhage—is observed in up to 40% of these cases.

44.6.3. Malignancy, lymphomatoid granulomatosis and malignant angioendothelioma

CNS disease in the context of Hodgkin's disease, with a pathological picture of isolated CNS angiitis, can occur. In malignant or neoplastic angioendotheliosis, the neoplastic process lies within the vascular lumen, and results from B-cell-derived lymphomatous cells which characteristically do not invade the vascular wall. The neurological features are similar to those of other cerebral microvasculopathic diseases, with superadded characteristic skin manifestations. Lymphomatoid granulomatosis, a nosologically separate disorder, is also lymphomatous and vasculopathic, but here there is a destructive inflammatory process centered on the vascular wall, lending the appearance of true vasculitis; the infiltrating neoplastic cell is of T-lymphocyte derivation. Cutaneous and pulmonary involvement is seen, with nodular cavitating lung infiltrates and neurological manifestations occurring in 25–30% of cases; they are the presenting feature in approximately 20%.

44.6.4. Drug and toxin-induced cerebral vasculitis

In most reports, there is no tissue confirmation of vasculitis, and the suggestion of "vasculitis" emerges only from angiography, despite widespread recognition that vasospasm can cause angiographic changes identical to those of vasculitis. In cocaine abuse, the significantly increased risk of ischemic stroke results from vasospasm (probably from increased catecholamine release), and very seldom from any form of vasculitis (Aggarwal et al., 1996). In intravenous abuse, co-injected contaminants such as hepatitis C may cause vasculitis. The most compelling evidence of a direct association relates to amphetamines, with clinical and histological evidence of multisystem necrotizing vasculitis (Citron et al., 1970). In humans, vasculitis may follow only a single dose of amphetamine but repeated exposure in young adults is the usual history.

Rarely, an immune reaction against (spontaneous) amyloid deposits within the cerebral vasculature appear to precipitate a true CNS vasculitis, a recently described disorder which has been termed Aß-related angiitis (ABRA) (Scolding et al., 2005).

44.7. The pathophysiology and pathogenesis of vasculitis

The neurological features of CNS vasculitis are those of ischemia and infarction, in turn resulting from the consequences of vascular wall inflammation: luminal obstruction, hypercoagulability from the effects of local proinflammatory cytokines (and other prothrombotic molecular changes on the endothelial surface), and alterations in vasomotor tone. The initiating immunological and inflammatory events of CNS vasculitis are extremely poorly understood, and there are no good animal models. However, the development of a vasculitic process depends on interplay between cellular and humoral immune factors, most research interest having classically centered on the latter (Jennette et al., 1994b)—though the point should be made that the conventional division of immune reactions into T-cell or B-cell (humoral) is of course misleadingly oversimplistic, since they are highly mutually interdependent.

Proving a definitive role for any immune mediator in any inflammatory disease is fraught with difficulty. In fact, of course, multiple mediators might all contribute, if not simultaneously then successively in the temporal evolution of specific disorders. Nonetheless, in some systemic vasculitides, a pathogenic role for anti-endothelial cell antibodies in injuring or (paradoxically) activating endothelial cells has been suggested (Salojin et al., 1996), though their lack of specificity and variable frequency of detection raise questions about any truly causal role. Rarely, an immune response against amyloid-beta deposits may precipitate cerebral vasculitis (Scolding et al., 2005).

Anti-neutrophil cytoplasmic antibodies (ANCAs) are a family of antibodies directed against constituents of the neutrophil azurophil granules (Mohan and Kerr, 2001); some suggest that these may play a direct role in generating tissue damage in vasculitis, and in maintaining vascular inflammation (Xiao et al., 2002; Harper et al., 2004). Certainly they have a very useful diagnostic role. Cytoplasmic ANCA (c-ANCA) targets proteinase-3 and is associated with near-95% specificity for Wegener's granulomatosis. Perinuclear ANCA (p-ANCA), directed at myeloperoxidase, is less specifically found in microscopic polyangiitis and Churg–Strauss syndrome (Mohan and Kerr, 2001).

Immune complexes can precipitate granuloma formation. Immune complex deposition in the blood vessel wall (of whatever cause) triggers complement activation, leading to polymorph and macrophage recruitment, amplification of inflammation, and the generation of lytic and injurious membrane attack complexes. Hepatitis B- and C-associated vasculitis are good examples of this process, with the latter found to underlie many cases of cryoglobulinemic vasculitis (Cacoub et al., 2001).

Increasing attention is directed towards T-cells as important mediators of vasculitis. In microscopic polyarteritis nodosa and in Wegener's granulomatosis, circulating T-cells responsive to PR-3 are found, and vascular lesions contain activated T-cells and antigen-presenting MHC class II positive dendritic cells (Mathieson and Oliveira, 1995). In primary CNS and peripheral nerve vasculitic lesions, the predominant infiltrate is one of $CD4^+$ and $CD8^+$ T-lymphocytes and monocytes (Lie, 1997a).

44.8. The treatment of medium- and small-vessel cerebral vasculitis

Symptomatic treatment is of course mandatory. Seizures may require anti-epileptic agents; the severely sick and immobile patient may need protection against venous thrombo-embolism, and kidneys and other organs should be monitored for involvement in any systemic vasculitic process. Hypertension in particular requires careful and prompt control.

Concerning specific therapy, quite why medium- and small-vessel CNS vasculitis requires such different therapy to large-vessel diseases is beyond this author's comprehension, but an incontrovertible body of evidence proves that steroids are sufficient induction in temporal arteritis, while most authorities firmly believe steroids alone are not an adequate therapy for confirmed medium- or small-vessel CNS vasculitis. Nonetheless, and although there have been no prospective controlled randomized treatment trials in medium- or small-vessel cerebral vasculitis (and neither are there likely to be any because of its rarity and the absence of unifying diagnostic criteria), this vasculitis is generally considered a highly treatable condition, rendering the problems in recognition and diagnosis of far more than mere academic importance. Retrospective reports, and extrapolations of lessons from systemic vasculitides (Jayne et al., 2003) support the use of steroids with cyclophosphamide in confirmed cases (Schmidley, 2000; Scolding et al., 2002).

Some authorities have suggested a separate CNS disorder be recognized, with a more favorable monophasic clinical course and carrying no requirement for such potentially toxic drugs. "Benign angiopathy of the CNS" is proposed as a subset of CNS angiitis, with normal, or near-normal CSF, and vasculitis suggested by angiography alone (Calabrese et al., 1993). The concept has been questioned in view of the obvious non-specificity of angiography, the fact that such cases as those reported (in not having proceeded to biopsy) are more likely to be the less severely affected, and because children satisfying "benign angiopathy" criteria often do not have a temperate, monophasic course, and have required aggressive immunotherapy (Gallagher et al., 2001). Most commentators, including the current author, believe a certain diagnosis of primary CNS angiitis must depend on positive biopsy, and that a vessel's morphological appearance on contrast angiography is no indicator of histology: only an 'angiopathy' can be diagnosed radiologically.

In biopsy-proven cerebral vasculitis, most would recommend an induction regime of high dose steroids—probably best as intravenous methyl prednisolone, 1 g daily for 3 days—followed by 60 mg/day oral prednisolone, decreasing by 10 mg at weekly intervals to 10 mg/day if possible. This should be coupled from the outset with cyclophosphamide 2.5 mg/kg (lower dose of 2 mg/kg in the elderly, or in renal failure) per day. This induction combination is suggested for 9–12 weeks. Daily oral intravenous cyclophosphamide and pulsed weekly treatment appear not significantly different in efficacy or toxicity. Careful monitoring of the blood count for evidence of bone marrow suppression should force a reduction of the cyclophosphamide dose if there is leucopenia (total white blood cell count falling to below 4.0×10^9) or neutropenia (below 2.0×10^9).

The importance of preventing, where possible, the adverse consequences of corticosteroids, in particular bone protection from osteoporosis, must be stressed. Gastric protection may be offered, and monitoring for the development of diabetes and hypertension are mandatory. Cyclophosphamide is associated with hemorrhagic cystitis (a complication reduced by adequate hydration and Mesna cover), a 33-fold increase in bladder cancer, other malignancies, infertility, cardiotoxicity, and pulmonary fibrosis. In a study of 145 patients treated with this agent for systemic Wegener's disease, and followed for a total of 1,333 patient-years, non-glomerular hematuria occurred in approximately 50%, the majority of whom had macroscopic changes consistent with cyclophosphamide-induced bladder injury on cystoscopy. Seven of these (and none without hematuria) developed transitional cell bladder carcinoma; six had had a total cumulative dose in excess of 100 g cyclophosphamide, and a duration

of oral treatment exceeding 2.7 years (Talar-Williams et al., 1996).

The maintenance phase of treatment, converting to a regime of alternate day steroids (10–20 mg prednisolone), and substituting azathioprine (2 mg/kg/day) for cyclophosphamide, is commenced after induction and continued for a further 10 months; it is then gradually withdrawn. Azathioprine is thought to be less toxic, but reversible bone marrow suppression can occur, hepatotoxicity is rare, and there is a small increased risk of malignancies.

Deterioration, failure to respond initially, or intolerance of the above regime may require the use of alternative agents. Methotrexate at 10–25 mg doses on a weekly basis may be used in conjunction with steroids, either during induction or maintenance. Intravenous immunoglobulin (0.4 mg/kg/day for 5 days), with its good safety record, has been found useful in cases of systemic vasculitis, though may induce only partial remission (Jayne et al., 2000). The recently confirmed efficacy of mycophenolate in severe lupus (Ong et al., 2005) may well imply comparable value in vasculitis.

Plasmapheresis may be valuable in cryoglobulinemia. It is also considered in severe life-threatening disease (e.g., pulmonary hemorrhage and severe glomerulonephritis) with 7–10 treatments over 14 days (Gaskin and Pusey, 2001). Although there is little experience of its use in patients with intracranial disease, there is evidence of significant improvement when used in combination with steroids in cerebral disease associated with Henoch–Schönlein purpura.

Monoclonal antibodies are of considerable promise. Anti-CD52 antibodies (an antigen present on most lymphocytes), anti-CD20 (B-cells) or tumor necrosis factor-blocking agents (directed against TNF itself or its receptor) are generating much excitement as novel therapies in various inflammatory diseases including the vasculitides, although paradoxically the induction of vasculitis has also been reported with some of these agents (Mathieson et al., 1990; Unger et al., 2003; Booth et al., 2004; Mohan et al., 2004; Sneller, 2005).

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Chapter 45

Hematological diseases and stroke

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45.1. Introduction

Management of cerebrovascular events is guided by the underlying etiology and is well studied for the established causes. However, in a significant proportion (particularly of young individuals) the origin of stroke remains unknown, or can be attributed to so-called "unusual" etiologies. Of these, strokes due to hematological disorders represent a non-negligible entity. This chapter delineates the existing evidence regarding the association of blood disorders with stroke. It summarizes the increasing information on the underlying pathophysiological mechanisms, as well as on treatment options.

Ischemic and hemorrhagic strokes, as well as sinovenous thromboses have been attributed to hematological disorders (Tables 45.1–45.3). Some hematological disorders have been shown to be causal, for others the association with cerebrovascular events is less certain because of the frequent co-existence of other vascular risk factors. The overall incidence of hematological disorders as cause of stroke is low, probably about 1% in adults. In younger age groups they may increase up to 10%. Extensive hematological evaluation of unselected patients will yield little useful information. Therefore, most stroke patients can be adequately evaluated with a routine hematological testing. A more thorough evaluation is warranted for patients with previous unexplained thrombotic episodes, combined venous and arterial thrombotic events, positive family history of recurrent thrombo-embolism, or patients with pathological laboratory findings. In patients with hereditary hematological disorders, studies should be extended to close relatives.

45.1.1. Coagulation and blood cells in hemostasis and thrombosis

The most remarkable characteristic of the hemostatic system is its capacity to maintain blood in the fluid state under physiological conditions until the integrity of blood vessels is disrupted. The formation of an impermeable platelet and fibrin plug must then remain localized to the site of vessel injury. This requires several anticoagulant mechanisms which control the powerful procoagulant substances. The initial comprehensive concept of a coagulation cascade of factors and cofactors has undergone extensive revision (Hoffman, 2003; Walsh, 2004; Dahlback, 2005).The recognition of the importance of platelet and other cell types in the coagulation process, and knowledge about the localization of coagulant reactions on specific cell surfaces lead to a more complex model of hemostasis. This is reviewed in detail in chapter 12. "Blood coagulation and fibrinolysis: mechanisms of thrombosis" of Stroke volume Part I.

Briefly, the initiation and propagation of blood coagulation are considered as a series of enzymatic reactions that occur on the plasma membranes of activated platelets, endothelial cells, and other intravascular cells (including monocytes and neutrophils), where all the involved enzymes, cofactors, and substrate molecules are located through exposure of cell membrane receptors (Fig. 45.1) (Hoffman, 2003; Walsh, 2004; Dahlback, 2005).

Red blood cells (RBC) participate in hemostasis by numerous mechanisms, chiefly by determining whole blood viscosity. A linear rise of hematocrit leads to a logarithmically increase of viscosity, thus promoting thrombosis (Grotta et al., 1986; Baskurt and Meiselman,

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Table 45.1

Blood cell disease and stroke

Red blood cell disorders			
	Dysfunction		
		Hemoglobin disorders	
			Sickle-cell disease
			Thalassemia
		Structural disorders	
			Nocturnal paroxysmal hemoglobinuria
			Spherocytosis
	Increased/decreased red blood cell count		
		Polycythemia vera	
		Secondary polycythemia	
		Anemia	
Platelet disorders			
	Functional disturbances		
		Acquired	
			Antiplatelet drugs
			Uremia
			Paraproteinemia
		Hereditary	
			Glanzmann's thrombasthenia
			Bernard–Soulier syndrome
			Sticky platelet syndrome
	Increased/decreased platelet count		
		Essential thrombocythemia	
		Reactive thrombocytosis	
		Thrombotic thrombocytopenic purpura (TTP)	
		Hemolytic uremic syndrome (HUS)	
		Idiopathic thrombotic thrombocytopenia (ITP)	
		Heparin induced thrombocytopenia (HIT)	
		Autoimmune thrombocytopenic purpura	
		Wiskott–Aldrich syndrome	
White blood cell disorders			
	Increased white blood cells		
		Acute nonlymphocytic leukemia (ANLL)	
		Acute lymphocytic leukemia (ALL)	
		Lymphoma (Hodgkin's/non-Hodgkin's)	
	Decreased white blood cells		
		Chronic familial cerebral vasculopathy	
Plasma cell disorders			
	Myeloma		
	Waldenström's macroglobulinemia		
	Cryoglobulinemia		

Table 45.2

Coagulation disorders and stroke

Bleeding disorders		
	Congenital	
		Factor VII deficiency (hemophilia A)
		Factor IX deficiency (hemophilia B)
		Von Willebrand's disease
		Afibrinogenemia
	Acquired	
		Acquired hemophilia
		Vitamin K deficiency
	Iatrogenic	
		Anticoagulants
		Thrombolytic agents
Thrombophilia		
	Antithrombotic proteins	
		Protein C deficiency
		Protein S deficiency
		Protein Z deficiency/increase
		Antithrombin III deficiency
		Heparin cofactor II deficiency
	Prothrombotic proteins	
		Factor V Leiden mutation (APC)
		Prothrombin gene mutation (G20210A)
		Elevated factors V, VII, VIII, vWF
		Elevated fibrinogen
	Fibrinolytic disorders	
		Plasminogen deficiency
		Dysfibrinogenemia
		Elevated plasminogen activator inhibitor 1
		Elevated tissue plasminogen activator
		Factor XII (Hageman factor) deficiency

APC = activated protein C resistance; vWF = von Willebrand factor.

Table 45.3

Various hematological disorders and stroke

Disseminated intravascular coagulation	
Antiphospholipid syndrome	
	Sneddon's syndrome
Hyperhomocysteinemia	
Hematological particularities in gynecology and obstetrics	
	Oral contraceptives use
	Hormone replacement therapy
	Pregnancy and puerperium

2003). The deformability of the RBC is another important factor affecting blood viscosity at the level of the microcirculation, where capillary diameter (4–6 μm) is in fact smaller than erythrocyte diameter (8 μm), and a decreased pliability results in "sludging" of RBC (Wood and Kee, 1985; Grotta et al., 1986; Andrews and Low, 1999; Baskurt and Meiselman, 2003). Increases in RBC aggregation, mainly in diseases due to alterations of the properties of membrane skeletal proteins, cell morphology, cytoplasmatic viscosity, and ratio of surface area to cell volume, can also lead to decreased blood fluidity (Andrews and Low, 1999; Baskurt and Meiselman, 2003). Beside the interference with viscosity, erythrocytes further modulate hemostasis by a variety of other mechanisms, such as control of platelet activity through altered levels of signal molecules, adherence to endothelium by expression of multiple membrane receptors on the cell surface, and, among others, catalysis of coagulation cascade activation by phosphatidylserine exposure (Andrews and Low, 1999; Baskurt and Meiselman, 2003).

Platelet adhesion, activation, and aggregation at sites of vascular endothelial disruption are key events

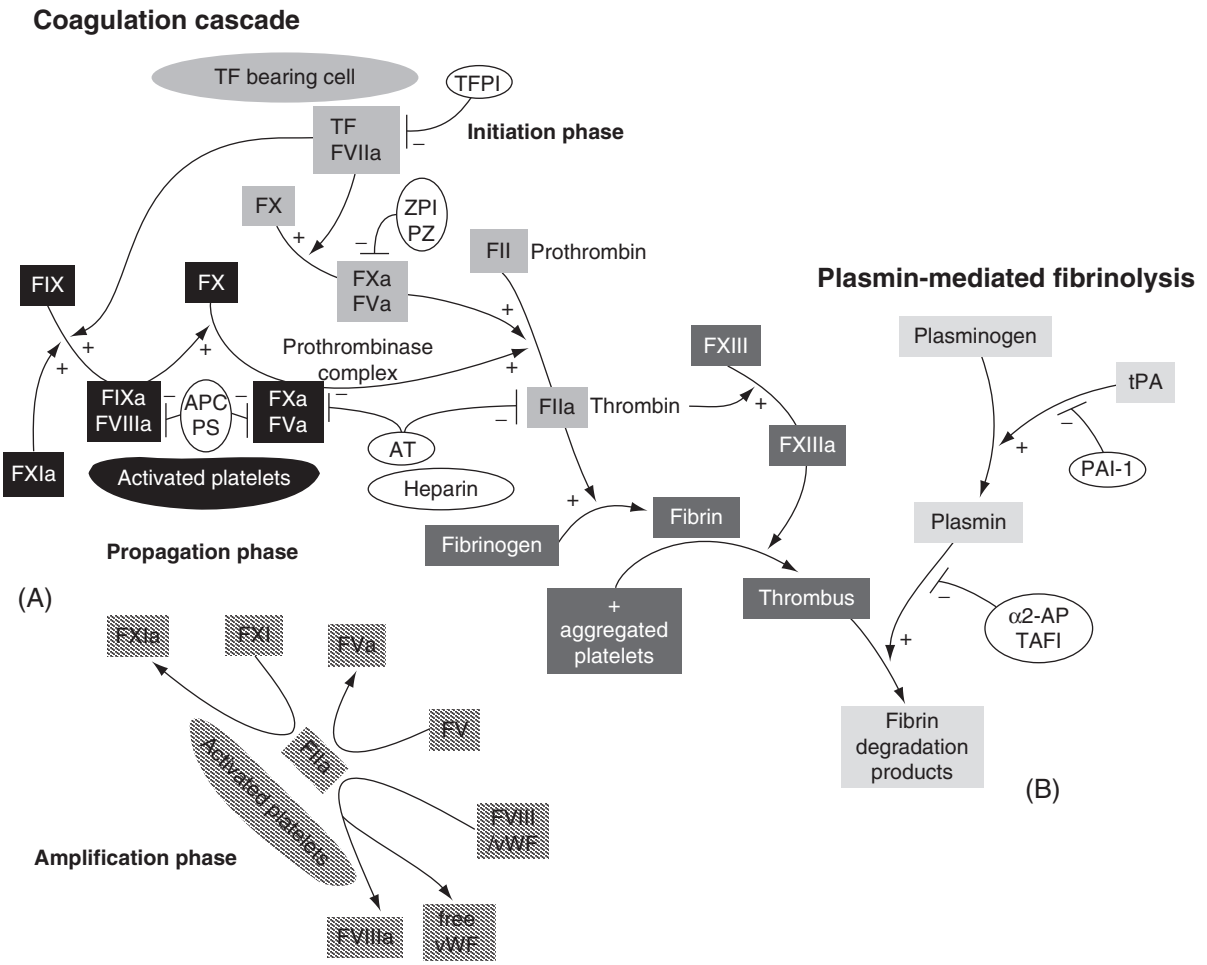


Fig. 45.1. Overview of blood coagulation. (A) The coagulation cascade is initiated by exposure of tissue factor (TF) at the site of endothelial injury, which binds to coagulation factor VIIa, leading to the conversion of prothrombin (factor II) to thrombin (factor IIa) by the prothrombinase complex (factor Xa and factor Va). The factor VIIa–tissue factor complex leads to the generation of small quantities of thrombin (factor IIa) by activation of factor V and factor X. The thrombin formation is amplified by other positive-feedback loops, referred to as propagation (via factor XIa, the tenase (factor VIIIa/IXa) and prothrombinase (factor Va/Xa) complexes) and amplification (activation of the cofactors V and VIII, and of small amounts of factor XIa). Subsequent cleavage of fibrinogen by thrombin and aggregation of activated platelets result in thrombus formation. The fibrin clot is further stabilized by factor XIIIa, which is also activated by thrombin. The clotting process is controlled at various steps. Any factor Xa that dissociates from the tissue factor-bearing cell is rapidly inhibited in the fluid phase by tissue factor pathway inhibitor and antithrombin, both always present bound to heparan sulfates expressed on the endothelial surface. The protein C/protein S/thrombomodulin (a membrane protein) system inactivates factor Va (and factor VIIIa) more efficiently on endothelial cells than on platelets, thus confining the formation of thrombin to the immediate area of an injury. Another inhibitory complex of protein Z (PZ) and the protein-Z-dependent protease inhibitor binds to the phospholipid surface and inhibits factor Xa production (Broze, 2001). (B) Finally, hemostasis is further regulated by plasmin-mediated fibrinolysis, following the conversion of plasminogen to plasmin by endothelium derived tissue-type plasminogen activator (tPA), and resulting in fibrin degradation products, and clot lysis. Plasminogen activator inhibitor 1 (PAI-1) rapidly inhibits tPA. Fibrinolysis is controlled by plasminogen activator inhibitor (PAI-1), α2-antiplasmin (α2-AP), and thrombin-activatable fibrinolysis inhibitor (TAFI).

in arterial thrombus formation. Particularly under high shear forces, platelet adhesion to the arterial wall is achieved through multiple high-affinity interactions between platelet membrane receptors (integrins) and ligands within the exposed subendothelium (Walsh, 2004; Dahlback, 2005; Eilertsen and Osterud, 2005). Platelets bind to exposed collagen via interaction with the platelet glycoprotein (GP) VI and GP Ia/IIb receptors, and indirectly through the platelet GP Ib-V-IX receptor via circulating von Willebrand factor. Platelet activation by exposed collagen and locally generated soluble platelet agonists (primarily thrombin, adenosine diphosphate (ADP), thromboxane A_2 (TxA_2), and serotonin) provides the stimulus for the release

of pro-inflammatory and procoagulatory substances stored in platelet α-granules and dense granules, including platelet-derived growth factors, chemotactic factors, and leukocyte-activating molecules. The released molecules are autocrine stimulators, further enhancing platelet activation and molecules that activate coagulation and other cell types, which finally results in the formation of a platelet-rich thrombus (Walsh, 2004; Eilertsen and Osterud, 2005).

White blood cells (WBC) also play an important role in the physiological process of hemostasis and in the mechanism of thrombus formation (Leone et al., 2001). Leukocytes express or release molecules with procoagulant or anticoagulant activity, such as tissue factor which can bind factor VIIa and initiate the hemostatic cascade (Altieri, 1995; Elstad et al., 1995). Furthermore, leukocytes cause functional alterations in vascular and perivascular cells (endothelial cells, platelets, other leukocytes) that in turn regulate blood coagulation. Thus, platelets can be modulated (through P-selectin, thrombospondin, or various integrins) or exposure of thrombogenic elastase is caused by enzymatic action on the endothelium (Eilertsen and Osterud, 2005). Finally, under particular conditions aggregating leukocytes are trapped and obstruct the microcirculation.

45.1.2. Epidemiology

The role of hematological disorders in ischemic and hemorrhagic stroke is currently fairly vague, since only a few prospective epidemiological studies addressed this issue. Some reviews summarize the knowledge of published case reports and small series of patients (Hart and Kanter, 1990; Weksler, 1995; Tatlisumak and Fisher, 1996; Quinones-Hinojosa et al., 2003). According to several retrospective analyses of prospectively collected stroke registry data, the percentage of blood disorders implicated in stroke varies from 0.5% to 15%, according to patient selection (e.g., age group <45 years) and included pathologies (Adams et al., 1995; Kristensen et al., 1997; Arboix et al., 2001; Bendixen et al., 2001; Gonthier and Bogousslavsky, 2004). In one prospective study, only 14 of 1,044 strokes (mean age 57 years) were considered as a manifestation of hematological disorders, representing 1% of all ischemic and hemorrhagic strokes in this institution. Ischemic strokes were more frequent (76%) than cerebral bleedings (14%), and hematological disorders represented the most common etiology (25%) of ischemic stroke of unusual cause. These findings are in agreement with experience from daily clinical practice, where only a minority of cerebrovascular events can be fully attributed to a hematological pathology. It also reflects the difficulty in establishing the precise cause of stroke in an individual patient, where concomitant risk factors are present. With larger epidemiological studies, increasing knowledge of the pathophysiological mechanisms of hematological diseases, and further improvement of diagnostic tests, it is likely that this group of disorders will gain greater importance in the management of stroke patients.

45.1.3. Features of stroke in hematological disorders

There is no common characteristic clinical presentation of stroke associated with hematological disorders. This is comprehensible because a wide variety of congenital or acquired hematological diseases can cause the same type of stroke, and, in contrast, the same blood disorder can be associated with ischemic infarction, cerebral hemorrhage, and even sinovenous thrombosis. Nevertheless, patients with cerebrovascular events of hematological origin are usually younger, and recurrence of stroke tends to be higher (Camerlingo et al., 2000; Arboix et al., 2001; Gonthier and Bogousslavsky, 2004). Whereas the underlying hematological disease may already be symptomatic at the time of occurrence of stroke, every cerebrovascular event can represent the first symptom of an underling blood disorder. Thus, particular emphasis should lie on the anamnestic hints (e.g., family history) and peculiar clinical presentation that can provide clues to diagnosis. The various blood disorders contributing to ischemic stroke or cerebral hemorrhage, and the clinical, diagnostic, and therapeutic implications are outlined in the following sections. The classification is arbitrary and, according to the applied criteria, may even overlap.

45.2. Blood cell diseases

45.2.1. Erythrocyte disorders

The importance of RBCs is not only their function to supply organs and tissues with oxygen, but also in the fact that erythrocyte abnormalities may themselves be the cause of cerebrovascular disease (Grotta et al., 1986; Andrews and Low, 1999). The role of RBCs in blood coagulation is discussed above. Numerous disorders of RBC are associated with stroke (Tables 45.1 and 45.4).

45.2.1.1. Sickle-cell disease

45.2.1.1.1. Overview

Sickle-cell disease is one of the most important hemoglobinopathies and the most prevalent form of congenital hemolytic anemia (Serjeant, 1997; Buchanan et al., 2004). It is characterized by a point mutation

Table 45.4

Red blood cell disorders and stroke

Disorder	Clinical Manifestation	Treatment (A = acute; P = preventive)	Evidence	Remarks
Sickle-cell disease	Macro ++	A: Simple/exchange transfusion	NA	For all pat
	Micro +++	P: Exchange transfusion	RT (Adams et al., 1998)	For pediatric risk pat <18years
		Hydroxyurea	US (Ware et al., 1999) (Sumoza et al., 2002)	For pediatric risk pat; adults?
		Bone marrow transplantation	US (Walters et al., 2000)	For selected pediatric risk pat
		Thrombolysis, anticoagulants, antiplatelet agents	NA	
	Hemorrhagic +	A: Supportive care	US	For all pat
		P: Surgery, endovascular treatment	CR (Anson et al., 1991) (McQuaker et al., 1999)	For all pat
	Sinovenous (+)	A/P: Anticoagulation	CR (Sebire et al., 2005)	
Thalassemia	Macro +	A: Supportive care	US (Borgna Pignatti et al., 1998)	
	Micro +	P: Anticoagulation, antiplatelet agents	NA	For risk pat (?)
	Hemorrhagic (+)	A: Supportive care	CR	
	Sinovenous (+)	A/P: Anticoagulation	CR (Sebire et al., 2005)	
Paroxysmal nocturnal hemoglobinuria	Macro (+)	A: Supportive care	CR	
		P: Anticoagulation/ Antiplatelet agents	NA	
	Venous +	A/P: Anticoagulation	CC (Hall et al., 2003)	All risk pat
Polycythemia vera	Macro ++	A: Supportive care	US	For all pat
	Micro ++	P: Phlebotomy, low-dose aspirin	CC (Pearson and Wetherley-Mein, 1978)	
		Hydroxyurea	RT (Landolfi et al., 2004)	For all pat
			RT (Kaplan et al., 1986)	For high risk pat
		Thrombolysis	NA	
	Hemorrhagic +	A: Supportive care	NA	
	Sinuvenous +	A/P: Anticoagulation	CR	For all pat; careful monitoring

Macro = territorial ischemic stroke
Micro = lacunar ischemic stroke
Hemorrhagic = hemorrhagic stroke
Sinuvenous = sinus/cerebral venous thrombosis
NA = no specific study on this issue
RT = randomized trial
CC = case control study
US = uncontrolled series
CR = case report
Pat = patients

in the sixth position of the beta-globin (β) gene on chromosome 11p15.5. Substitution of glutamic acid (Glu) for valine (Val) results in an abnormal globin chain: β^S (Ingram, 1956). "Sickle hemoglobin" is a type of hemoglobin consisting of two normal α and two β^S chains around a heme molecule ($\alpha_2\beta^s{}_2$). Upon deoxygenation, β^S aggregate to form rod-like polymers. As a consequence, the normally pliable RBC assumes a rigid, sickled shape, where the term "sickle cell" is derived from. Erythrocyte membrane damage and hemolysis ensue if this process is not reversed with oxygenation. Finally, through increased blood viscosity and cellular adhesion, vascular occlusion and ischemic damage in the dependent tissue results (Embury, 1986; Bunn, 1997; Buchanan et al., 2004).

Inheritance of two β^S genes leads to homozygous sickle-cell disease, or sickle-cell anemia (HbSS). People who carry just one β^S mutation have the sickle-cell trait (HbAS), and are generally asymptomatic (Serjeant, 1997). In sickle hemoglobin, a mutation in the β gene results in substitution of glutamic acid (Glu) by lysine (Lys) leading to β^C. Further mutations of b gene have been described (β^{Lepore}, $\beta^{O\text{-}Arab}$, $\beta^{D\text{-}Punjab}$, etc.). Other genotypes that give rise to sickle-cell disease include double heterozygous states in which the β^S gene is inherited together with other abnormal genes, or with mutations that result in decreased synthesis of β genes (e.g., β-thalassemia). The HbSC genotype is the most common double heterozygous state, followed by HbSb-thalassemia (Steinberg, 1984; Chui and Dover, 2001). A higher concentration of sickle hemoglobin in erythrocytes (in HbSS >85% of hemoglobin, in HbAS 25–45%, and in HbSC ~50%) promotes the tendency of polymerization, whereas the presence of other hemoglobins, HbF ($\alpha_2\gamma_2$) and HbA_2 ($\alpha_2\delta_2$), protects cells from sickling (Embury, 1986; Bunn, 1997).

The largest proportion of sickle-cell disease occurs among blacks due to survival advantage of people with sickle-cell trait in case of infections with *Plasmodium falciparum* (Aidoo et al., 2002). In some parts of Africa 45% of the population is heterozygous for the β^S gene, whereas in the USA and the Caribbean about 8% of blacks carry one β^S gene. The β^S gene also occurs in Asia, the Mediterranean basin, Saudi Arabia, and India (Chui and Dover, 2001).

Whereas heterozygous individuals frequently have no clinical manifestations even into adulthood, the presentation of HbSS patients is highly variable. It is characterized by disease onset in infancy, hemolytic anemia, an increased susceptibility to infection and vaso-occlusion. These occur in almost all vascular beds leading to ischemic tissue injury manifesting as painful episodes (abdomen, chest, bone), and finally to organ dysfunction and early death (Bunn, 1997; Serjeant, 1997; Buchanan et al., 2004). The median age of death for HbSS is 42/48 years (males/females, respectively) and in HbSC 60/65 years, whereas with sickle trait mortality is not increased (Powars et al., 1978).

45.2.1.1.2. Stroke and sickle-cell disease

Stroke is one of the most serious complications in sickle-cell disease patients. Ischemic infarction accounts for 75% of strokes (Adams et al., 2001). It occurs in 11% of patients with homozygous sickle-cell disease by the age of 20 years (mean age of first stroke is 7.7 years), and the rates in children are particularly high (Ohene-Frempong et al., 1998). Radiographic evidence of small infarction without clinical symptoms is referred to silent infarction. With an incidence of 15–25%, silent infarctions are increasingly recognized as the major form of neurological injury and cause for cognitive problems in children (Bernaudin et al., 2000; Kirkham et al., 2000; Pegelow et al., 2002). Hemorrhagic stroke (of which 1–2% are subarachnoid hemorrhages) is more prevalent in younger adults with a mean age of 25 years (Powars et al., 1978; Ohene-Frempong et al., 1998). Cerebral venous thrombosis can also occur (van Mierlo et al., 2003), but is rare (Table 45.4).

The usual presentation of stroke in sickle-cell disease is a focal deficit, most often hemiparesis, monoparesis, or aphasia. Ictal seizures have also been reported with a high incidence, whereas sensory or visual disturbances are likely to be missed in young children. Severe headache and altered level of consciousness are more typical of intracranial hemorrhage (Adams et al., 2001).

Cerebral infarction results from various mechanisms, mainly from obstruction of the microcirculation by sickled RBC or vasculopathy of larger intracranial arteries with stenosis. Thereby, ischemia is the result of post-stenotic perfusion failure or occlusion by artery-to-artery embolism (Embury, 1986; Adams et al., 2001). Adhesive interactions between activated vascular endothelial cells, erythrocytes, leukocytes, and platelets promote the vaso-occlusive process through changes of blood viscosity. Also, pro-inflammatory state, hypercoagulability, and endothelial dysfunction seem to contribute to sickle-cell vaso-occlusion (Makis et al., 2000; Frenette, 2002). It is postulated that macroangiopathy is the result of obstruction of the vasa vasorum, and of mechanical damage of endothelium by sickle cells (Stockman et al., 1972). In the majority of sickle-cell disease patients, large-vessel disease affects the internal carotid or the middle and anterior cerebral arteries, thus explaining the moyamoya pattern of collateral vessels

sometimes seen in HbSS (Stockman et al., 1972; Adams et al., 2001). Strokes most frequently affect the cerebral cortex and white matter of both hemispheres, especially in the watershed area of the anterior and middle cerebral arteries, whereas other localizations (basal ganglia, thalamus, cerebellum, brainstem, spinal cord, etc.) are less often involved.

The recurrence rate of stroke in individuals with HbSS is high (in untreated patients between 50–80%) (Powars et al., 1978), but can be reduced dramatically by therapy. Since disease severity and survival are strikingly variable and treatment burdensome, numerous investigations have focused on the identification of risk factors and elaboration of prediction models to further optimize treatment strategies. Known risk factors for stroke include low HbF concentration, low hemoglobin levels, leukocytosis, nocturnal hypoxemia, the β globin haplotype, α-thalassemia, and possibly elevated homocysteine levels (Serjeant, 1997; Ohene-Frempong et al., 1998; Kirkham et al., 2000; Adams et al., 2001; Chui and Dover, 2001; Aidoo et al., 2002; Buchanan et al., 2004; Quinn and Miller, 2004; Steinberg, 2005; Hoppe, 2005). Adams et al. demonstrated the utility of transcranial Doppler ultrasonography (TCD) in primary stroke prevention, where abnormally increased TCD velocities predict stroke, albeit not in all cases (Adams et al., 1998). Also brain magnetic resonance imaging (MRI) might be useful to identify patients at risk for stroke. Alongside prior stroke as the strongest risk factor for further events, silent infarctions in children with HbSS have been shown to increase the incidence of subsequent new overt stroke by 14-fold (Miller et al., 2001). Since the confirmation of familial risk of stroke in HbSS (Driscoll et al., 2003), increasing interest has been attributed to the molecular genetic basis of stroke risk in sickle-cell disease. Polymorphisms in many genes associated with adhesion, thrombophilia, inflammation and regulation of blood pressure have been identified, which possibly affect the phenotype of stroke in sickle-cell disease (Hoppe, 2005; Steinberg, 2005). Recently, a new promising predictive model of overt stroke in sickle-cell disease was generated, using Bayesian networks to analyze variations in 108 single-nucleotide polymorphisms of 39 candidate genes (Sebastiani et al., 2005).

45.2.1.1.3. Diagnosis and treatment

Ischemic stroke only rarely represents the first clinical manifestation of sickle-cell disease, in so far as diagnosis should be suspected in patients presenting with hemolytic anemia or any associated clinical syndromes (as painful episodes of chest, abdomen, and bones, dactylitis, osteonecrosis, cholelithiasis, renal dysfunction, or proliferative retinopathy). Basic hematological investigations for the diagnosis of sickle hemoglobin include full blood counts, Hb analysis by electrophoresis, isoelectric focusing and/or high-performance liquid chromatography and quantification of HbA_2 and HbF levels. Supplementary investigations comprise the evaluation of iron status and functional tests for Hb variants that may modify the presentation of the disease. More sophisticated biochemical tests or molecular biology investigations may be necessary (Clark and Thein, 2004). In individuals with confirmed sickle-cell disease, MRI may be used to screen for silent infarctions, whereas magnetic resonance angiography (MRA) and TCD allow detection and quantification of relevant large intracranial artery stenosis (Adams et al., 1998; Seibert et al., 1998; Miller et al., 2001; Pegelow et al., 2002). These two non-invasive techniques reduce the need for cerebral angiography, which carries a small risk of worsening sickle-cell disease (Richards and Nulsen, 1971; Rao et al., 1985).

The primary treatment of sickle-cell disease includes vaccinations and early use of antibiotics to prevent infections (Gaston et al., 1986; Steinberg, 1999). Painful episodes are supported by administration of fluid, oxygen, and analgesics. If indicated, electrolyte imbalance should be corrected. Folate is often prescribed to prevent megaloblastic erythropoiesis (Rabb et al., 1983) and may help to reduce one potential risk factor by lowering the homocysteine levels. Management of acute ischemic stroke includes imaging studies as a first step to rule out hemorrhage. Since thrombolytic therapy has not yet been tested in stroke associated with sickle-cell disease, mainly supportive measures are taken (hydration, oxygenation, and correction of anemia by RBC transfusions) (Steinberg, 1999; Adams et al., 2001; Buchanan et al., 2004). It is also uncertain whether antiplatelet agents or anticoagulants are of any value (Table 45.4). Whereas the use of exchange transfusion in acute stroke is unstudied, chronic transfusion therapy is the most effective, although not perfect, in prevention of first and recurrent ischemic strokes in children with HbSS (Russell et al., 1984; Pegelow et al., 1995; Adams et al., 2001; Buchanan et al., 2004). The standard recommendation is to maintain sickle hemoglobin at 30% for the first 3 years after stroke, and if the patient remains neurologically stable, at 50% afterwards (Cohen et al., 1992). By chronic transfusion therapy the risk of stroke decreases to about 10% (Russell et al., 1984); however, this therapy is cumbersome, the optimal duration is not known, and transfusion-related complications, such as alloimmunization, infections (hepatitis C, AIDS) and iron overload, are of major concern (Steinberg, 1999). Many

experimental pharmacological therapies with the purpose of increasing HbF-levels or of changing RBC deformability, have been, and are being studied. Only hydroxyurea has been shown to reduce recurrence rate of stroke in patients in whom chronic transfusion therapy was discontinued for various reasons, and even in very young children this possible benefit of hydroxyurea was recently confirmed (Ware et al., 1999; Gulbis et al., 2005). Long-term hydroxyurea treatment bears the risk of malignancy, and other significant side-effects are known, limiting the use of hydroxyurea to severely affected patients (Buchanan et al., 2004). Despite impressive disease amelioration, allogenic bone marrow transplantation as a curative treatment for sickle-cell disease is reserved for highly selected patients. In stroke patients who have undergone successful transplantation only a few neurological complications (post-transplant intracranial hemorrhage and seizures) have been reported (Walters et al., 1995). New developments in bone marrow transplantation and gene therapy are being explored, but are not likely to benefit patients in the near future (Vichinsky, 2002).

Treatment of hemorrhagic stroke in sickle-cell disease is not uniform. Ruptured aneurysms are surgically clipped or treated by endovascular coil embolization (McQuaker et al., 1999). Chronic transfusion therapy has been used to manage children with hemorrhagic stroke, but it has not been reported as a widespread practice in adult patients (Steinberg, 1999; Buchanan et al., 2004).

45.2.1.2. Thalassemia

Thalassemia is a congenital hemolytic disorder primarily found in individuals of Mediterranean descent. It is caused by a partial or complete deficiency in the synthesis of hemoglobin subunits. In α-thalassemia there is impaired production of alpha-globin (α) chains, in β-thalassemia of beta-globin (β) chains (Cohen et al., 2004). The thalassemias involve a large clinical spectrum ranging from subtle morphologic changes of RBCs in asymptomatic patients to a life-threatening disease. Homozygous or double heterozygous carriers of β-gene defects suffer from severe anemia and other serious complications from early childhood (β-thalassemia major, β-TM, and b-thalassemia intermedia, β-TI). "Hb H disease" is used to denote patients with deletions of three of four α-genes usually having Hb H, a tetramer composed of four β chains (β_4).

Recently, the evidence of a chronic hypercoagulable state in thalassemic patients has been summarized (Eldor and Rachmilewitz, 2002). It is based on an increased incidence of thrombo-embolic events and the existence of prothrombotic hemostatic anomalies. Deep venous thrombosis, pulmonary embolism, sinovenous thrombosis (Sebire et al., 2005), and recurrent arterial occlusions have been described mainly in patients with β-TM and β-TI. The incidence varies from 1.1% to 29%, mainly reflecting the selection of patients and their respective treatment in these studies (Borgna Pignatti et al., 1998; Moratelli et al., 1998; Cappellini et al., 2000). Stroke or TIA are reported in 0.02% and 20%, respectively, of thalassemic patients, who clinically present with headache, seizures, and hemiparesis (Logothetis et al., 1972; Borgna Pignatti et al., 1998). In asymptomatic individuals with β-TI, a high frequency (37%) of brain damage including ischemic brain lesions was detected by magnetic resonance imaging (MRI) (Manfre et al., 1999). Cerebro-embolic events have also been reported in α-thalassemia, as well as cerebral hemorrhage following blood transfusion in four β-TM patients (Eldor and Rachmilewitz, 2002).

The proposed mechanisms of thrombogenesis in thalassemia are multifold. They include ongoing activation of platelets, monocytes, granulocytes, and endothelial cells, low levels of proteins C and S, increased levels of activation peptides, and findings consistent with continuous thrombin generation (Eldor and Rachmilewitz, 2002). Specific changes in the membrane of RBC and hemosiderosis may further contribute to the activation of the coagulation process.

Thalassemia is treated with chronic blood transfusion and iron chelators to prevent iron overload resulting in progressive organ failure (Cohen et al., 2004). The addition of prophylactic antithrombotic therapy has only recently been suggested for high-risk patients and those who already had developed a thrombotic event (Cappellini et al., 2000; Eldor and Rachmilewitz, 2002; Cohen et al., 2004). However, recommendations are not uniform and controlled studies are lacking (Table 45.4).

45.2.1.3. Paroxysmal nocturnal hemoglobinuria

Paroxysmal nocturnal hemoglobinuria is a rare genetic disorder of the bone marrow characterized by intravascular hemolysis, venous thrombosis and aplastic anemia. It affects men and women equally, and presents usually before the age of 30 years (Hillmen et al., 1995; Socie et al., 1996). It is caused by the clonal expansion of genetically altered stem cells. Mutation in the pig-a gene disrupts the synthesis of glycosylphosphatidylinositol (GPI) and therefore the expression of GPI-anchored membrane proteins on the surface of progeny erythrocytes, leukocytes, and platelets. The deficiency of two GPI-linked membrane proteins with complement (C′)-regulatory activities, CD55 and CD59, renders affected RBCs in paroxysmal nocturnal hemoglobinuria sensitive to C′-mediated hemolysis (Rosti, 2000; Hall et al., 2002; Rosse et al., 2004; Young, 2005). This

chronic intravascular hemolysis and hemoglobinuria can be accentuated during sleep or be induced by infection, surgery, and blood transfusion. Such attacks are associated clinically with abdominal or back pain, malaise, and fever. Pancytopenia, marrow hypoplasia, and iron deficiency are other concomitant findings (Hillmen et al., 1995; Socie et al., 1996).

The cause of the thrombotic tendency in paroxysmal nocturnal hemoglobinuria is not entirely clear. It probably results from platelet activation and aggregation by complement, coupled with the release of thromboplastin from hemolysed RBCs (Rosse et al., 2004; Young, 2005). Venous thrombosis has a predilection for the intra-abdominal and cerebral veins. Cerebral venous thrombosis, mostly of the superior sagittal, lateral, cavernous sinus, or of cortical veins, has in some cases been linked to onset of estrogen therapy or with pregnancy (Stirling et al., 1980; Wozniak and Kitchens, 1982; Donhowe and Lazaro, 1984; al-Hakim et al., 1993). There are only a few reports of arterial cerebrovascular events (al-Samman et al., 1994; von Stuckrad-Barre et al., 2003; Audebert et al., 2005). The diagnostic test for paroxysmal nocturnal hemoglobinuria is the analysis of GPI-linked molecules on the surface of hematopoietic cells by flow cytometry, whereas tests of C′-sensitivity may only be useful as screening methods (Richards et al., 2000).

The principal therapy for paroxysmal nocturnal hemoglobinuria is supportive care with, for example, transfusions, iron supplementation, or corticosteroids, as required, and the treatment of complications. The standard of care after established venous thrombosis in paroxysmal nocturnal hemoglobinuria is life-long full anticoagulation, whereas the value of a primary prophylaxis is unclear (Hall et al., 2003). Warfarin is also indicated for treatment of cerebral venous thrombosis in paroxysmal nocturnal hemoglobinuria. There are no studies of antiplatelet drugs, such as aspirin or clopidogrel, in paroxysmal nocturnal hemoglobinuria. Patients with cytopenia due to associated aplastic anemia will often respond to immunosuppressive therapy with antithymocyte globulin and/or cyclosporine, whereas the hemolytic anemia may be treated with monoclonal anti-C5 antibodies (Hillmen et al., 2004). The only curative strategy, allogenetic stem cell transplantation, should only be considered in selected cases because of a considerable risk of mortality and possible spontaneous remission in about 15% of patients with paroxysmal nocturnal hemoglobinuria (Hillmen et al., 1995; Saso et al., 1999).

45.2.1.4. Hereditary spherocytosis

Hereditary spherocytosis, elliptocytosis and pyropoikilocytosis represent a group of genetic disorders that are due to deficiency or dysfunction of one of the RBC membrane skeletal proteins (spectrin, actin, protein 4.1, or ankyrin) (Palek, 1987; Tse and Lux, 1999; Iolascon et al., 2003; Gallagher, 2004). Six genetic loci and various genetic defects have been identified. This genetic heterogeneity goes together with the variability of clinical and laboratory manifestations. The various disorders are characterized by hemolysis or splenic sequestration of defective RBCs, leading to anemia, splenomegaly, and jaundice. Hereditary spherocytosis and elliptocytosis can be complicated by thrombosis, frequently after splenectomy, and mostly involve mesenteric and portal veins (Hayag-Barin et al., 1998). A few patients with hereditary spherocytosis and stroke have also been reported (van Hilten et al., 1989; Schilling, 1997; Tokunaga et al., 2001). Antithrombotic therapy is empiric.

45.2.1.5. Diamond-Blackfan anemia

Diamond-Blackfan anemia is a congenital hypoproliferative anemia known to be associated with diverse physical anomalies affecting the thumb, craniofacial bones, urogenital system, and heart. There has been an anecdotic report of associated cerebral ischemia (Butrum et al., 2003).

45.2.1.6. Severe iron deficiency anemia

Rarely, severe iron deficiency anemia has been recognized as a cause of ischemic stroke or cerebral venous thrombosis in adult or pediatric populations (Belman et al., 1990; Akins et al., 1996; Swann and Kendra, 2000). The main cause is intestinal blood loss, but inadequate dietary iron intake is rare in Western countries. Several potential pathophysiological mechanisms are hypothesized. Thrombocytosis occurring in iron-deficiency anemia is thought to be the major contributing factor of venous thrombosis. In ischemic stroke, rheological changes due to decreased blood viscosity may lead to turbulent flow, damage of endothelium, and platelet aggregation. Finally, microcytosis is associated with a reduction in the red cell deformability, which could facilitate small-vessel thrombosis (Belman et al., 1990; Akins et al., 1996; Swann and Kendra, 2000).

45.2.1.7. Polycythemias

45.2.1.7.1. Polycythemia vera

Polycythemia vera is the only acquired form of primary erythrocytosis (Table 45.3), although some familial cases with a suspected genetic cause have been reported (Cario et al., 2003). Polycythemia vera is a myeloproliferative disorder characterized by the clonal expansion of mainly erythroid, but also myeloid, and megakaryocytic cell lines (Adamson et al., 1976; Pearson et al., 2000; Spivak, 2002). Onset is insidious, occurring in middle-aged or elderly individuals (median age 57–60 years, only 5% $<$40 years)

with an incidence of about 0.2–20 per 10 million per year (Osgood, 1965; Najean et al., 1998; Kutti and Ridell, 2001). Median survival is relatively long (about 15 years) and the rate of transformation into either acute leukemia or myelofibrosis is low (10–15% within 15 years) (GISP—Gruppo Italiano Studio Policitemia, 1995; Finazzi et al., 2005). However, the clinical course is complicated by frequent thrombohemorrhagic episodes. Thrombosis (arterial > venous > microcirculatory) is more frequent than bleeding. Thrombo-embolic complications, particularly cerebral and myocardial infarction, occur in about 12–39%, and hemorrhages (gastrointestinal and cerebrovascular) in 1.7–20%, respectively (Bilgrami and Greenberg, 1995; Landolfi et al., 1995; Pearson et al., 2000; Spivak, 2002; Elliott and Tefferi, 2005). Deep venous thrombosis of the lower legs with pulmonary embolism accounts for the majority of venous thrombotic events, followed by portal or hepatic localization of thrombosis (GISP—Gruppo Italiano Studio Policitemia 1995; Barbui and Finazzi, 2003; Elliott and Tefferi, 2005). Other symptoms, such as headache, paresthesiae, dizziness, blurred vision, tinnitus, and erythromelalgia, are thought to result from disturbed microcirculation due to elevated blood viscosity and platelet activation (Spivak, 2002; Elliott and Tefferi, 2005).

Cerebrovascular accidents mostly involve large and small arterial territories and watershed areas. Ischemic stroke precedes the diagnosis of polycythemia vera not uncommonly and represents a leading cause of morbidity and mortality (Silverstein et al., 1962; GISP - Gruppo Italiano Studio Policitemia, 1995; Landolfi et al., 1995; Spivak, 2002; Elliott and Tefferi, 2005). Besides arterial, venous thrombosis and cerebral bleeding (intracerebral hemorrhage, subdural and subarachnoidal bleeding) have also been reported (Table 45.4).

Thrombosis in polycythemia vera is thought to result from raised whole blood viscosity and both qualitative and quantitative platelet changes (Pearson, 1997). The hematocrit mainly depends on the cellular blood components, whereby a linear rise of hematocrit leads to a logarithmically increase of viscosity. Together with elevated arterial oxygen content, which leads to further adjustments of vessel diameters, blood flow decreases. Under these conditions the width of the mural plasmatic zone is reduced, which increases the possibility of platelet activation, platelet–platelet contact and platelet–vessel wall interaction, particularly when the platelet count is raised as well. These effects increase the likelihood of the initiation of thrombus formation in polycythemia vera (Pearson, 1997; Elliott and Tefferi, 2005). The mechanisms predisposing to bleeding are more obscure and beside platelet dysfunction, often the use of anticoagulants or antiplatelet agents may be involved (Elliott and Tefferi, 2005).

Diagnosis according to the WHO criteria is based on the combination of various clinical (splenomegaly, absence of hypoxic lung/heart disease), hematologic (elevated red cell mass/hemoglobin levels, leuko- and thrombocytosis), biochemical (erythropoietin), biological (endogenous erythroid colony formation, clonality) parameters, and bone marrow histology. However, the diagnostic criteria are imperfect (Thiele and Kvasnicka, 2003). PRV-1 mRNA overexpression, quantitatively assessed by real-time polymerase chain reaction, was recently introduced as a molecular marker for polycythemia vera and other myeloproliferative disorders, and may discriminate between polycythemia vera and erythrocytosis of other origin (Temerinac et al., 2000; Klippel et al., 2003). Other new potential biomarkers (e.g., Mpl mRNA) are currently being evaluated (Bock et al., 2004; Pahl, 2004).

To date, there is no curative treatment for polycythemia vera, thus the current rationale for using drugs is to treat or prevent thrombosis or bleeding (Pearson et al., 2000; Spivak, 2002; Tefferi, 2003; Barbui et al., 2004; Elliott and Tefferi, 2005). Since the risk of thrombosis in patients with polycythemia vera correlates with the hematocrit, phlebotomy to reduce the hematocrit to $<45\%$ in male and $<42\%$ in females remains the cornerstone of therapy for all patients with erythrocytosis and mild thrombocytosis (Pearson et al., 2000; Spivak, 2002; Tefferi, 2003; Barbui et al., 2004; Elliott and Tefferi, 2005). Additional cytoreductive therapy is used according to the risk of thrombotic complications, which has been shown to be significantly higher in patients with advanced age (≥ 60 years) or a history of previous thrombosis (GISP—Gruppo Italiano Studio Policitemia, 1995; Spivak et al., 2003). Further vascular risk factors predicting survival and cardiovascular mortality were smoking habit and diabetes (Spivak et al., 2003). The platelet count per se is not correlated with incidence of thrombosis, but the risk of bleeding increases with platelet counts exceeding $1{,}000 \times 10^9$/l. Therefore platelet count is not used to guide treatment aiming at prevention of thrombo-occlusive events, but may be considered for patients at risk for bleeding. Cytotoxic therapy is indicated in high-risk patients (defined as age ≥ 60 years, at least one previous thrombotic event) (see Table 45.2). The drug of choice is hydroxyurea because its leukemogenicity is low or non-existent (Kaplan et al., 1986; Nand et al., 1996; Najean and Rain, 1997; Pearson et al., 2000; Spivak et al., 2003). There is no evidence that an additional cytoreductive therapy is needed in low risk situations (age <60 years, no history of thrombosis, no cardiovascular risk factors). New therapeutic options, theoretically devoid of leukemic risk, such as alpha-interferon, anagrelide, and imatinib, should be

reserved for selected patients and require further clinical experience (Lengfelder et al., 2000; Oehler et al., 2003; Fruchtman et al., 2005). A recent controlled study has demonstrated the efficacy of low-dose aspirin (100 mg per day) in adults with polycythemia vera to reduce both arterial and venous thrombotic events. Bleeding complications in patients treated with aspirin were not increased compared to the placebo group (Landolfi et al., 2004). Except for contraindications to aspirin and for extreme thrombocytosis, low-dose aspirin can safely prevent thrombotic complications and is therefore recommended for high- and low-risk patients (Elliott and Tefferi, 2005). There are no sufficient data on alternative antiplatelet agents to allow any conclusion to their value. Anticoagulation for venous thrombosis with warfarin must be closely monitored (Elliott and Tefferi, 2005).

45.2.1.7.2. Secondary polycythemias

Secondary polycythemias depend on hormonal factors (predominantly erythropoietin) extrinsic to the erythroid compartment (Prchal, 2003; Van Maerken et al., 2004). The increased erythropoietin secretion may represent a physiological response to tissue hypoxia from, for example, cyanotic heart disease, chronic pulmonary disease, cirrhosis, and hydronephrosis. It can also result from an abnormal autonomous erythropoietin production (e.g. hemangioblastoma) or a dysregulation of oxygen-dependent erythropoietin synthesis (e.g., mutations in the von Hippel-Lindau gene). Secondary congenital erythrocytoses are listed in Table 45.5. Systematic data on the clinical presentation, laboratory evaluation, and on treatment are sparse. The clinical spectrum ranges from asymptomatic patients or mild hyperviscosity related symptoms (headache, dizziness, blurred vision) to manifest thrombohemorrhagic complications (Prchal, 2003; Van Maerken et al., 2004). Overall, the secondary polycythemias are less frequently associated with thrombosis than polycythemia vera, which is thought to depend mainly on different rheological factors (Pearson, 2001). Reports of ischemic stroke or cerebral hemorrhage are rare, and especially for reactive secondary polycythemia the causality is difficult to establish because other major cardiovascular risk factors are frequently present as well (Jaillard et al., 1995).

Table 45.5

Primary and secondary erythrocytosis

Primary erythrocytosis			
	Congenital	Primary familial and congenital polycythemia (PFCP)	
	Acquired	Polycythemia vera	
Secondary erythrocytosis			
	Congenital	Abnormal Hb with high oxygen affinity	
		2,3-bisphosphoglycerate deficiency	
		Chuvash polycythemia	
		Sporadic or familial erythrocytosis with VHL-gene mutation	
	Acquired	Reactive erythropoietin elevation in arterial hypoxemia	
			High altitude, cyanotic heart disease, Chronic lung disease, smoking
		Renal lesions	
			Cysts, diffuse parenchymal disease, Hydronephrosis
		Hepatic lesions	
			Hepatitis, cirrhosis
		Autonomic erythropoietin synthesis of various tumors	
			Hepatoma, renal tumors, cerebellar hemangioblastoma
		Drugs	
			Androgens

VHL = von Hippel-Lindau.

45.2.2. Platelet disorders

Platelet disorders can be classified with regard to aberrations in platelet number (thrombocytosis, thrombocytopenia) or function, both defects being either inherited or, more commonly, acquired. Besides distinct thrombocyte disorders, numerous medical conditions affect production, function and lifespan of platelets (e.g., liver disease, chronic renal failure, cancer, etc.). Thus, a wide variety of disorders exist, representing independent factors for ischemic or hemorrhagic strokes in all age groups (Tables 45.1 and 45.6). The role of platelets in the maintenance of hemostasis have briefly been described earlier in this chapter.

45.2.2.1. Essential thrombocythemia and thrombocytosis

Like polycythemia vera, essential thrombocythemia is a chronic myeloproliferative disorder characterized by bone marrow hyperplasia, excessive proliferation of megakaryocytes, and a sustained elevation of the platelet count ($> 800 \times 10^9$/l) in the peripheral blood

Table 45.6

Platelet disorders and stroke

Disorder	Clinical Manifestation	Treatment (A = acute/P = preventive)	Evidence	Remarks
Essential thrombocythemia	Macro +	A: Supportive care	US	For all pat
	Micro ++	P: low-dose aspirin	CC (Jensen et al., 2000)	For all pat
		Hydroxyurea	RT (Cortelazzo et al., 1995) (Harrison et al., 2005)	For high risk pat, age >40years
		Thrombolysis	NA	
	Hemorrhagic (+)	A: Supportive care	CR	
	Sinuvenous +	A/P: Anticoagulation	US	For all pat; careful monitoring
Thrombotic thrombocytopenic purpura	Macro (+)	A: Plasma exchange	RT (Rock et al., 1991)	For all pat
	Micro +	Splenectomy	US (Onundarson et al., 1992)	For treatment refractory pat
	Hemorrhagic (+) Sinuvenous –	A: Plasma exchange	US	For all pat
Idiopathic thrombocytopenic purpura	Hemorrhagic +	A: Corticosteroids,	US (Lee and Kim, 1998)	For all pat
		Intravenous immune globulin (IVIG)	(Medeiros and Buchanan, 1998)	
Heparin induced thrombocytopenia	Macro + Micro (+)	A: Argatroban, hirudine followed by anticoagulation	US (Lewis et al., 2001) (Greinacher et al., 1999)	For all pat
	Venous (+)	Thrombolysis	NA	

Macro = territorial ischemic stroke
Micro = lacunar ischemic stroke
Hemorrhagic = hemorrhagic stroke
Sinuvenous = sinus/cerebral venous thrombosis
NA = no specific study on this issue
RT = randomized trial
CC = case control study
US = uncontrolled series
CR = case report
Pat = patients

(Tefferi et al., 1995; Spivak et al., 2003; Elliott and Tefferi, 2005). Essential thrombocythemia has been thought to arise from a clonal abnormal pluripotent stem cell (Anger et al., 1990), but recent studies have demonstrated that a substantial number of cases classified as essential thrombocythemia may not be clonal (< 50% of patients with x-chromosome inactivation pattern) (Harrison et al., 1999). Some, but not all studies report a gender predilection (male:female ratio of 1:2). The age of occurrence is usually between 50 and 70 years (mean 60 years). Children can also be affected (Mesa et al., 1999; Jensen et al., 2000; Spivak et al., 2003; Elliott and Tefferi, 2005). There are only sporadic reports on malignant transformation in essential thrombocythemia (e.g., acute myeloid leukemia) (Andersson et al., 2000).

The major clinical features of essential thrombocythemia are arterial, venous, and microcirculatory thrombotic and rarely hemorrhagic events. However, many ischemias and hemorrhages remain asymptomatic. The reported prevalence of thrombosis and bleeding is variable, ranging from 14% to 86%, and the annual incidence is 6.6% (Cortelazzo et al., 1990; Fenaux et al., 1990; Tefferi et al., 1995; Jensen et al., 2000; Sacchi et al., 2000; Elliott and Tefferi, 2005). Platelet count seems not to predict thrombosis, but paradoxically a thrombocytosis $>1500 \times 10^9$/l is considered a risk factor for bleeding (Fenaux et al., 1990; van Genderen et al., 1994; Besses et al., 1999; Elliott and Tefferi, 2005). As in polycythemia vera, risk factors for thrombosis in essential thrombocythemia patients are age of over 60 years and a history of previous thrombosis (Cortelazzo et al., 1995; Besses et al., 1999; Elliott and Tefferi, 2005). Venous thrombosis particularly involves the lower limbs, and splanchnic (e.g., Budd–Chiari syndrome) and cerebral veins (see Table 45.6). Large-vessel occlusion mainly affects the cerebral circulation and coronary arteries. The most prevalent circulatory symptoms reported reflect disturbances of microcirculation (headache, dizziness, dysesthesiae). Also erythromelalgia is a syndrome, which presents with unilateral or bilateral asymmetric erythema, congestion, and burning pain of the hands and feet. It is attributed to microvascular thrombosis (Cortelazzo et al., 1990; Michiels, 1997; Besses et al., 1999; Jensen et al., 2000; Kesler et al., 2000; Elliott and Tefferi, 2005).

Structural and functional platelet abnormalities as well as platelet membrane receptor anomalies mainly contribute to the pathophysiology of thrombosis. For example, the sustained release of thromboxane A2 has been hypothesized to induce vasoconstriction and platelet aggregation. Furthermore, polymorphonuclear cells may be involved in the pathogenesis of thrombophilic states through endothelial damage and coagulation system activation (Falanga et al., 2000; Spivak et al., 2003; Elliott and Tefferi, 2005). Bleeding has been attributed to an acquired von Willebrand syndrome, where the loss of large von Willebrand factor multimers, through a yet unclear mechanism, would lead to a von Willebrand disease-like bleeding tendency (van Genderen et al., 1994; Elliott and Tefferi, 2005).

The therapeutic strategy in essential thrombocythemia is a difficult balance between the prevention of thrombosis and bleeding complications, and the risk of side-effects or toxicity of drugs. Since arterial thrombosis accounts for the most deaths in essential thrombocythemia patients, a cytoreductive therapy is indicated in high-risk patients (age >60 years, at least one previous thrombotic event) (Barbui and Finazzi, 2003; Spivak et al., 2003; Barbui et al., 2004; Elliott and Tefferi, 2005). Hydroxyurea has emerged as the treatment of choice, since efficacy has been confirmed in a randomized trial with a significant reduction of overall thrombotic events with tolerable side-effects (anemia, neutropenia, cutaneous ulcers) (Cortelazzo et al., 1995). Furthermore, the leukemogenicity seems very low (Finazzi et al., 2000). The risk of thrombosis in asymptomatic low-risk patients may not be high enough to warrant the use of potentially mutagenic or toxic cytoreductive therapy. Recently, the data from a randomized trial comparing hydroxyurea plus aspirin versus anagrelide plus aspirin in high-risk essential thrombocythemia have been published. The patients treated with anagrelide plus aspirin were more likely to withdraw from therapy due to side-effects and showed higher rates of arterial thrombosis or serious hemorrhage (Harrison et al., 2005). Despite high cost, alpha-interferon remains an alternative agent for cytoreductive treatment in essential thrombocythemia, especially for women in childbearing age, since the drug does not pass the placenta (Barbui and Finazzi, 2003; Spivak et al., 2003; Barbui et al., 2004; Elliott and Tefferi, 2005). Although not prospectively confirmed and with the exception of a previous history of bleeding or a platelet count $>1500 \times 10^9$/l, antiplatelet therapy (100 mg per day of aspirin) has been shown to safely reduce the incidence of thrombosis in essential thrombocythemia and to effectively control microvascular symptoms (Michiels, 1997; Jensen et al., 2000). There are too few data available on alternative antiplatelet agents to draw any conclusion on their value in essential thrombocythemia. Platelet apheresis is an effective and relatively safe means of rapidly reducing the platelet count in the short term and has been successfully used for myeloproliferative disorder-associated

acquired von Willebrand syndrome (van Genderen et al., 1997).

Diagnosis of essential thrombocythemia is mainly done by exclusion of reactive thrombocytosis, which predominantly occurs with iron deficiency anemia. Severe infections, chronic inflammatory diseases (e.g., sarcoidosis), rheumatic diseases (rheumatoid arthritis, polyarteritis nodosa, giant cell arteritis) may also lead to reactive thrombocytosis. However, thrombotic complications are rare (Schafer, 2004).

45.2.2.2. Thrombotic thrombocytopenic purpura

Thrombotic thrombocytopenic purpura is counted among the thrombotic microangiopathies, severe disorders characterized by platelet aggregation, microthrombi formation and resulting tissue damage (Table 45.7). Thrombotic thrombocytopenic purpura is a rare disease, with an incidence of about 0.1–3.8 per million per year, and is most common in the third and fourth decade of life. Women are affected nearly twice as often as men (George et al., 2004; Miller et al., 2004; Sadler et al., 2004). The classic features ("pentad") of thrombotic thrombocytopenic purpura are microangiopathic hemolytic anemia (with $>1\%$ schistocytes on the blood smear), severe thrombocytopenia (usually less than $10–20 \times 10^9$/l), neurological manifestations, renal abnormalities (e.g., hematuria, proteinuria), and fever (Moake, 2002; Kremer Hovinga et al., 2003; Sadler et al., 2004; Mayer and Aledort, 2005). A prominent laboratory feature consists of extremely elevated serum levels of lactate dehydrogenase as a consequence of hemolysis and lactate dehydrogenase release from ischemic or necrotic tissue cells (Moake, 2002; Sadler et al., 2004; Mayer and Aledort, 2005).

Table 45.7

Causes of thrombotic microangiopathies

Medications	
	Quinine
	Ticlopidine
	Clopidogrel
	Cyclosporin
	Tacrolimus
	Cisplatin
Stem cell transplantation	
HIV infection	
Pregnancy	
Autoimmune diseases	
	Systemic lupus erythematosus (SLE)
	Ankylosing spondylitis
	Sjögren's syndrome
	Polyarteritis nodosa
	Polymyositis
Malignancy	
	Adenocarcinoma of breast, gastrointestinal tract and lung
Shiga toxins	
Idiopathic enzyme deficiency	

Ischemia in thrombotic thrombocytopenic purpura originates from impaired microcirculation due to vessel obstruction by platelet thrombi. Thereby, altered vascular surfaces and shear forces lead to fragmentation of erythrocytes (Brain et al., 1962; Rubenberg et al., 1967). Only recently unusually large von Willebrand factor multimers have been identified as the cause of platelet clumping (Moake et al., 1982). Von Willebrand factor is a multimeric glycoprotein composed of identical disulfide-linked 250 kD subunits, which plays an important role in platelet adhesion to the subendothelium of damaged vessel walls (Arya et al., 2002). It is synthesized by endothelial cells and megakaryocytes and secreted in the form of extremely adhesive ultra-large von Willebrand factor multimers into the circulation. There they are degraded by a specific plasmaprotease, the thirteenth member of a family of metalloproteases—ADAMTS-13 (a disintegrin and metalloprotease with thrombospondin type 1 motif) (Furlan et al., 1996; Tsai, 1996; Zheng et al., 2001). Most patients with classical thrombotic thrombocytopenic purpura have a severely deficient activity of this von Willebrand factor-cleaving protease (often $<5\%$ of normal) (Furlan et al., 1998; Tsai and Lian, 1998). Impaired cleavage of ultra-large von Willebrand factor multimers leads to the formation of platelet thrombi (Sadler et al., 2004). Today, two forms of classical thrombotic thrombocytopenic purpura are distinguished. Hereditary thrombotic thrombocytopenic purpura (Upshaw–Schulman syndrome) is caused by severe constitutional deficiency of ADAMTS-13. Today, over 70 different ADAMTS-13 mutations have been reported of which two-thirds are missense mutations (Levy et al., 2001; Schneppenheim et al., 2003; Kokame and Miyata, 2004; Matsumoto et al., 2004; Sadler et al., 2004). Acquired idiopathic thrombotic thrombocytopenic purpura is caused by circulating neutralizing ADAMTS-13 autoantibodies (mainly IgG). Besides an idiopathic form, pregnancy, stem cell transplantation, thienopyridine (ticlopidine or clopidogrel), and other associated forms of acquired thrombotic thrombocytopenic purpura also have been described (Moake, 2002; Vesely et al., 2003; George et al., 2004; Sadler et al., 2004; Mayer and Aledort, 2005).

Although a generally good agreement concerning the identification of severely deficient ADAMTS-13

activity between different assays exists, difficulties in utilizing the protease activity as a diagnostic test remain (Studt et al., 2003). In patients with characteristic presenting features and clinical course of thrombotic thrombocytopenic purpura, only moderate decreased or even normal (> 50%) levels of ADAMTS-13 activity can be measured. In contrast, asymptomatic individuals can reveal severe ADAMTS-13 deficiency (Kremer Hovinga et al., 2003; Vesely et al., 2003; Sadler et al., 2004). The evaluation of patients with suspected thrombotic thrombocytopenic purpura is further complicated by a variable clinical presentation. None of the "classic" symptoms (fever, petechial hemorrhages, abdominal pain, arthralgias, myalgias, neurological signs, renal involvement) are mandatory for diagnosis. Thus, in a patient with symptoms compatible with thrombotic thrombocytopenic purpura, thrombocytopenia, schistocytosis, and a highly elevated serum LDH value are sufficient to suggest a diagnosis of thrombotic thrombocytopenic purpura in clinical praxis (Moake, 2002).

The most frequent complications in thrombotic thrombocytopenic purpura involve the nervous system. Neurological manifestations are the presenting symptom in about 50% of patients and occur in 90% during the course of the disease. These are in order of frequency headache, confusion or altered mental state, paresis, aphasia, seizures, cranial nerve palsies, and ataxia (Ridolfi and Bell, 1981; Vesely et al., 2003; George et al., 2004; Sadler et al., 2004; Mayer and Aledort, 2005). Ischemic cerebral infarction and cerebral hemorrhage occur in about 10%. Neuroimaging usually reveals small cortical or subcortical infarcts, due to the preferential involvement of the microcirculation, but occlusion of large intracranial arteries has also been described (Ben-Yehuda et al., 1988; Rinkel et al., 1991; Tardy et al., 1993; Scheid et al., 2004). Even severe neurologic impairment can fully recover with early and aggressive treatment.

Plasma exchange therapy has dramatically improved survival of patients with acute thrombotic thrombocytopenic purpura from < 10% to about 80–90%. It is now considered the standard treatment (Bell et al., 1991; Rock et al., 1991; Kremer Hovinga et al., 2003; Fontana et al., 2004; Sadler et al., 2004; Scheid et al., 2004; Mayer and Aledort, 2005). The rationale is the removal of autoantibodies against ADAMTS-13, ultra-large von Willebrand factor multimers and other potentially detrimental factors by plasmapheresis and the replacement of absent or defective metalloprotease by fresh frozen or cryodepleted plasma. Regarding the use of glucocorticoids and other immunosuppressive agents (interferon alpha, cyclophosphamide, azathioprine), or intravenous immunoglobulin, respectively, current clinical practice is inconsistent. Also the role of splenectomy in relapsing thrombotic thrombocytopenic purpura and refractory cases is based on anecdotal rather than controlled studies (Moake, 2002; Sadler et al., 2004; Mayer and Aledort, 2005). New and promising experimental treatments include the humanized monoclonal antibody to CD20, rituximab, in cases of resistant thrombotic thrombocytopenic purpura, and recombinant ADAMTS-13 for hereditary thrombotic thrombocytopenic purpura (Ahmad et al., 2004; Plaimauer and Scheiflinger, 2004). Aspirin may provoke hemorrhagic complications in patients with severe thrombocytopenia (Rosove et al., 1982).

45.2.2.3. Hemolytic uremic syndrome

Hemolytic uremic syndrome shares many of the features of thrombotic thrombocytopenic purpura, such as thrombocytopenia, microangiopathic hemolytic anemia, and fever. By contrast, renal failure is the predominant finding at presentation, whereas neurological manifestations are rare (Moake, 2002; Sadler et al., 2004; Mayer and Aledort, 2005). Hemolytic uremic syndrome mostly affects children, with an age at diagnosis < 20 years. The incidence is estimated to be 6.7 per million per year, and the disease occurs more frequently in females (Miller et al., 2004). The differing histopathologies (predominantly fibrin-containing thrombi) (Hosler et al., 2003) and pathophysiologic pathways led to the recognition of hemolytic uremic syndrome as a separate disease entity. The two elucidated pathomechanisms are toxin production by bacteria (shiga-like toxins or verotoxines of *Escherichia coli* serotypes, *Shigella dysenteriae*, or rarely other microbes) and inappropriate regulation of the complement system by deficient or defective factor H (that inhibits complement activation via the alternative pathway) (Boyce et al., 1995; Rougier et al., 1998; Moake, 2002; Mayer and Aledort, 2005). Endothelial damage with the release of cytokines results in platelet aggregation and leads to thrombus formation. Ischemic stroke, most commonly involving the basal ganglia and thalami, as well as cerebral hemorrhage have been reported, mostly microangiopathic lesions as seen in MRI (Hahn et al., 1989; Siegler et al., 1994; Theobald et al., 2001; Garg et al., 2003). Treatment mainly consists of appropriate management of renal failure and the avoidance of aggravating medications (antimotility agents and paradoxically antibiotics). Plasma infusion or exchange therapy has been tried with various results. Purified or recombinant factor H may be helpful in familial hemolytic uremic syndrome with a deficiency of factor H. It is not known whether anticoagulation treatment is effective and safe (Moake, 2002).

45.2.2.4. Idiopathic thrombocytopenic purpura

Immune thrombocytopenic purpura is an autoimmune disease characterized by mucocutaneous bleeding and low platelet count, occurring with an annual incidence of about 100 cases per million persons (Frederiksen and Schmidt, 1999; Cines and Blanchette, 2002; Cines et al., 2004). Childhood-onset immune thrombocytopenic purpura is a mostly self-limiting acute illness following an infection, whereas immune thrombocytopenic purpura in adults is usually chronic with insidious onset and a female predilection (Cines and Blanchette, 2002). Immune thrombocytopenic purpura is caused by production of self-reactive IgG antibodies against one or more platelet surface glycoproteins (GP), including GPIIb-IIIa, GPIb-IX, GPIa-IIa, among others. Platelet-bound autoantibodies can be detected with a sensitivity of 49–66% and a specificity of 78–93%, helping to support diagnosis with regard to other thrombocytopenias (McMillan, 2003). Antibody-coated platelets are destroyed by either phagocytosis, predominantly in the spleen, or complement-induced lysis. Furthermore, platelet production in the bone marrow may also be impaired by autoantibodies (McMillan, 2000; Cines and Blanchette, 2002; Cines et al., 2004). Early studies reported an increased incidence of *H. pylori* infection in immune thrombocytopenic purpura patients and persistent partial or complete remissions in many patients following its eradication, which could not be confirmed by a recent prospective study (Michel et al., 2004). The major cause of fatal bleeding in patients with immune thrombocytopenic purpura is intracranial hemorrhage. Intracerebral hemorrhage and subdural hematoma are rare complications (in 0.2–1% of cases) predominantly of the acute severe form of immune thrombocytopenic purpura, occurring at a platelet count generally below 10×10^9/l (Lilleyman, 1994; Lee and Kim, 1998; Frederiksen and Schmidt, 1999; Cines and Blanchette, 2002; Butros and Bussel, 2003). Contributing risk factors include head trauma and exposure to antiplatelet drugs. Most intracranial hemorrhages occur within 4 weeks after presentation with immune thrombocytopenic purpura, but only 10% within the first 3 days after diagnosis (Lilleyman, 1994; Butros and Bussel, 2003). Treatment is usually required in adults, whereas it remains controversial for children with acute immune thrombocytopenic purpura because outcome is favorable even without therapy. The goal of treatment is to raise the platelet count into a hemostatically safe range. This is achieved primarily by corticosteroids, but also intravenous immune globulin, whereas splenectomy and other treatment modalities (rituximab, cyclophosphamide, azathioprine, cyclosporine, mycophenolate mofetil, or vincristine) are reserved for refractory cases (Cines and Blanchette, 2002; Cines et al., 2004; Rosse et al., 2004) (see Table 45.6). Experimental therapies include platelet growth factors or stem-cell transplantation (Cines et al., 2004).

45.2.2.5. Heparin-induced thrombocytopenia

Irradiation, ethanol, portal hypertension, prosthetic cardiac valves and numerous other pathological conditions are associated with a low platelet count. Drugs also represent an important cause of acquired thrombocytopenia (George et al., 1998; Greinacher et al., 2001). Besides the cytotoxic effects of anti-tumor therapy, various drug-induced and drug-dependent immune mechanisms can lead to enhanced platelet destruction (Greinacher et al., 2001). Some possible causative agents are listed in Table 45.8. By far, the most frequent type of immune-mediated thrombocytopenias related to drugs is heparin-induced thrombocytopenia. Estimates on the incidence range from 1% to 5% in patients receiving intravenous unfractionated heparin, or 0.8% with subcutaneous low-molecular-weight heparins, surgical patients being at highest risk (Warkentin et al., 1995; Greinacher et al., 2001; Girolami et al., 2003; Cines et al., 2004). Heparin-induced thrombocytopenia is an acquired immune-mediated disease characterized

Table 45.8

Medications associated with thrombocytopenia

Cytotoxic agents	Cyclophosphamide, fluorouracil, methotrexate
Cinchona alkaloids	Quinidine, quinine
Antimicrobial agents	Trimethoprim-sulfamethoxazole, amphotericin B, rifampicin
Antiepileptics	Carbamazepine, phenytoine, valproate acid
Non-steroidal anti-inflammatory drugs	Diclophenac, indomethacin
Heparine	
Miscellaneous	Gold-salt, procainamide, digoxin, amiodarone, furosemide, cimetidine, rituximab

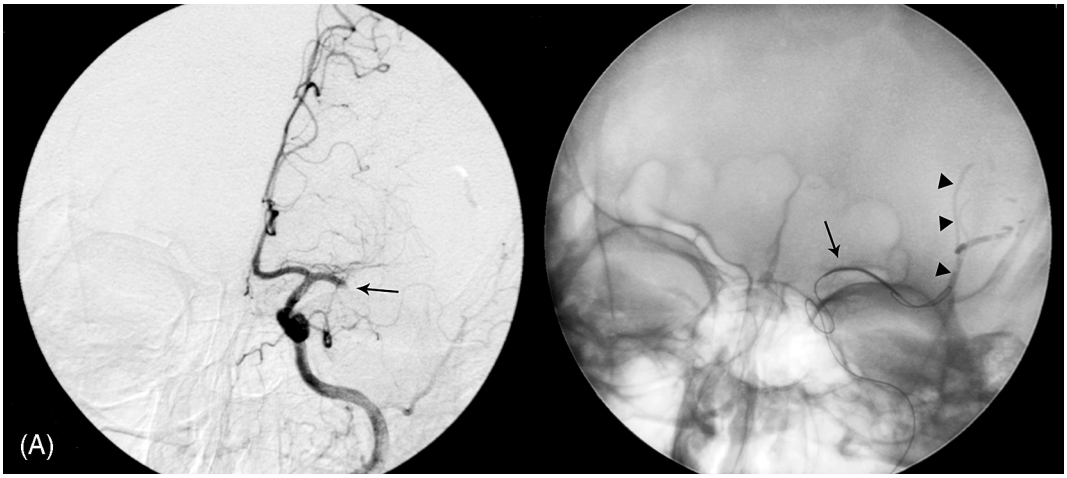
A more comprehensive list is available at http://moon.ouhsc.edu/jgeorge

by a "paradoxical" hypercoagulable state with increased thrombin generation and elevated risk of venous and arterial thrombo-embolism (Greinacher et al., 2001; Warkentin, 2003; Cines et al., 2004; Franchini, 2005). Almost all individuals with heparin-induced thrombocytopenia have antibodies to heparin-platelet factor 4 (PF4) complexes in their plasma, with those with high titer IgG responses being at greatest risk of developing clinical disease. IgG/heparin-PF4 complexes activate platelets through the platelet Fc receptor, resulting in further PF4 release and amplification of this process. In addition, thrombin activation follows from liberation of platelet-derived microparticles, and possibly also from activation of endothelial cells and monocytes (Amiral et al., 1992; Warkentin et al., 1994; Greinacher et al., 2001; Warkentin, 2003; Cines et al., 2004; Franchini, 2005). In heparin-induced thrombocytopenia, the platelet count typically drops by more than 50% from baseline, often to less than 150×10^9/l, beginning 5–14 days after starting heparin. In patients with recent previous heparin exposure platelet count can decrease earlier. Morbidity and mortality in heparin-induced thrombocytopenia are related to thrombotic events, with venous thrombosis occurring most commonly (with 40% pulmonary embolism). The type of arterial thrombosis in order of frequency is limb artery thrombosis, thrombotic stroke (Fig. 45.2A–C), and myocardial infarction. Thrombosis develops in up to 50% of heparin-induced thrombocytopenia patients and is generally managed by heparin cessation alone (Wallis et al., 1999). Besides ischemic stroke, neurological complications include transient confusional states and cerebral venous thrombosis (Meyer-Lindenberg et al., 1997; Pohl et al., 1999; LaMonte et al., 2004). Heparin-induced thrombocytopenia remains a clinical diagnosis, supported by confirmatory laboratory testing. Demonstration of heparin-induced thrombocytopenia antibodies is possible by immunologic assays (usually ELISA kits measuring the presence of anti-heparin-PF4 antibodies of all antibody classes) or by platelet-activation assays (available only at specialized centers) (Warkentin, 2002). For managing heparin-induced thrombocytopenia, heparin should be discontinued immediately and alternative anticoagulation should be initiated. Although used successfully in some patients, danaparoid cross-reacts with more than 10% of heparin-induced thrombocytopenia antibodies. The direct thrombin inhibitors argatroban and lepirudin lack cross-reactivity with these antibodies and have been shown in prospective studies to improve clinical outcomes in heparin-induced thrombocytopenia (Warkentin, 2003; Cines et al., 2004; Hirsh et al., 2004; Franchini, 2005). A recent retrospective analysis showed a significant reduction of new stroke and stroke-associated mortality in argatroban-treated patients with heparin-induced thrombocytopenia versus controls without increase of intracranial hemorrhage (LaMonte et al., 2004). Warfarin is not recommended as an acute treatment because it can paradoxically worsen the thrombosis and cause venous gangrene (Warkentin et al., 1997). Since most patients with a history of heparin-induced thrombocytopenia show an anamnestic response when re-exposed to heparin, both unfractionated heparin and low-molecular-weight heparin should be avoided, except for short-term treatment in special clinical settings (Warkentin, 2003; Cines et al., 2004; Hirsh et al., 2004; Franchini, 2005). Antiplatelet agents, although not assessed systematically as other adjunctive treatments, might be beneficial in patients with heparin-induced thrombocytopenia, but bear the risk of bleeding as well. In addition to surgical thrombectomy, regional or systemic thrombolysis should also be considered in patients with limb-threatening thrombosis or pulmonary embolism with severe cardiovascular compromise (Greinacher et al., 2001; Hirsh et al., 2004). Whether thrombolysis can safely be performed in acute stroke and heparin-induced thrombocytopenia is not known (Fig. 45.2A–C, Table 45.6).

45.2.2.6. Rare platelet disorders

Henoch–Schönlein purpura (HSP) is an immune complex-mediated generalized small-vessel vasculitis, characterized by vascular wall deposits of predominantly IgA, typically involving small vessels in the skin, gut, joints, and kidneys. Henoch–Schönlein purpura is associated with palpable cutaneous purpura, intestinal colic, arthralgia, and hematuria. The nervous system may be involved, but manifestations are usually mild and transient (e.g., headache, behavioral alterations, and reduction in the level of consciousness) (Ostergaard and Storm, 1991). Intracerebral and subarachnoid hemorrhage have been reported rarely as severe complications resulting from cerebral vasculitis (Chiaretti et al., 2002). Plasmapheresis has been used in Henoch–Schönlein purpura cerebral vasculitis with intracerebral hemorrhage with anecdotally good success (Wen et al., 2005).

Neonatal alloimmune thrombocytopenia can occur when a mother is immunized against fetal platelet antigens inherited from the father. Five major human platelet antigen (HPA) systems are capable of causing this disorder (most frequently HPA-1a). Early diagnosis and appropriate platelet transfusion therapy are essential to prevent life-threatening intracranial hemorrhage in the thrombocytopenic fetus or neonate (Rothenberger, 2002). Table 45.9 lists some inherited platelet disorders. Stroke has been rarely reported (Hart and Kanter, 1990; Gaspoz et al., 1995; Mammen, 1999; Cines et al., 2004).



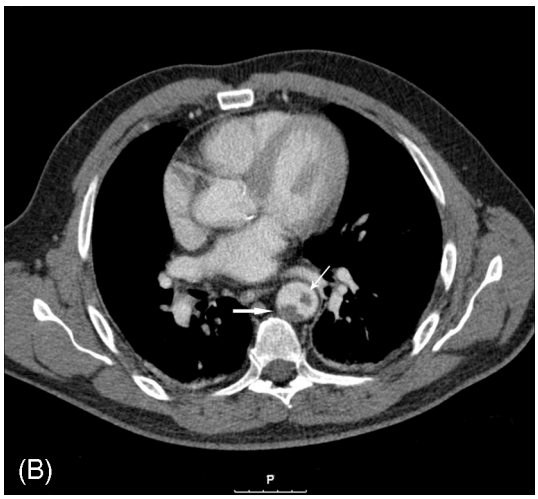


Fig. 45.2. Case report of stroke in heparin-induced thrombocytopenia. In a 59-year-old patient a treatment with heparin and warfarin was initiated due to thrombosis of the left vena saphena magna. Fourteen days later, he was admitted to the emergency department with an acute aphasia and right-sided hemiplegia. CT scan 2 hours after symptom onset did not show any early signs of ischemic infarction, but CT perfusion revealed severe hypoperfusion of the entire vascular territory of the left middle cerebral artery. The thrombotic occlusion of the proximal middle cerebral artery (M1) was confirmed by cerebral angiography, which was carried out in view of an intra-arterial thrombolysis treatment. At that time, the information on pre-existing anticoagulation and the laboratory findings (INR of 2.5, thrombocytopenia of 38×10^9/l) came to light. Thus, the procedure was limited to a mechanical recanalization of the middle cerebral artery, which was partially successful (TIMI 2). Ischemic infarction remained confined mainly to the left insular region. The patient's motor functions improved considerably, whereas aphasia and apraxia persisted 1 year later. Diagnostic workup confirmed heparin-induced thrombocytopenia, the heparin-P4-antibody assay being significantly elevated. (A) Left panel shows digital subtraction angiography showing the thrombotic occlusion of the patient's left proximal middle cerebral artery (arrow); right panel shows the balloon catheter at the side of obstruction (arrow), as some of the major distal branches of the middle cerebral artery, which in part are filled by injected contrast agent (rectangles). (B) Thoracic CT contrast-agent-enhanced cross-section of CT depicting a floating (small arrow) as well as adherent thrombi (larger arrow) in the patient's descending aorta.

(Continued)

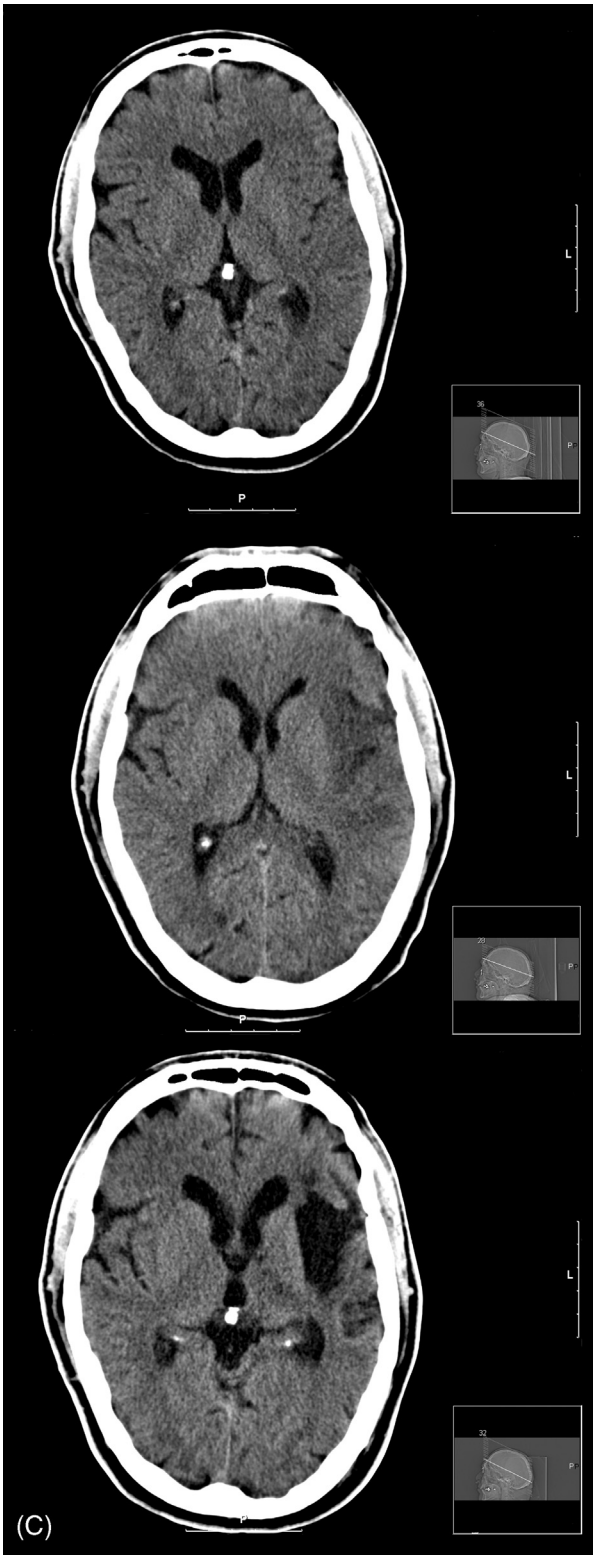


Fig. 45.2. Cont'd. (C) Serial cerebral CT scans. The patient's scans at admission (top panel), 1 day after mechanical recanalization of the left middle cerebral artery (middle panel), and 1 year after the ischemic stroke (bottom panel) are shown. Ischemic infarction is confined to the left insular and part of the frontal cortex.

45.2.3. Disorders of white blood cells and plasma cells

The role of white blood cells (WBC) in coagulation has been summarized in 45.1.1. The potential relevance of leukocytes in thrombosis is supported by epidemiological studies showing a correlation between white blood cell count and the risk of myocardial infarction and ischemic stroke (Ernst et al., 1987; Koren-Morag et al., 2005). Not infrequently, disorders of WBC are also accompanied by an increased risk for cerebrovascular complications. The mechanisms that could contribute to a stroke only are rudimentaryly understood. The most important oncohematologic diseases are described below (see Table 45.1).

45.2.3.1. Leukemias and lymphomas

Involvement of the nervous system in lymphoreticular malignancies is the consequence of therapeutic procedures (e.g., radiation therapy, chemotherapy), complications of immunosuppression (infections), or manifestations of the primary disease (involvement by the malignancy, cerebrovascular complications). Intracranial hemorrhage, ischemic infarction, and cerebral sinus thrombosis occur in patients with leukemia and lymphoma as a result of leukocytosis, thrombocytopenia, coagulopathy, sepsis, or treatment (Demopoulos and DeAngelis, 2002; Recht and Mrugala, 2003).

45.2.3.1.1. Leukemias

Acute myeloid leukemias and acute lymphoid leukemias (Harris et al., 1999) often present with similar clinical features, like pallor, fatigue, dyspnea on mild exertion, hepato-splenomegaly with abdominal discomfort and nausea, bleeding, skin changes, and fever, often due to infections. Clues to diagnosis include pancytopenia, leukocytosis, and/or circulating blasts. All types of acute leukemia are associated with intracranial hemorrhage and, less frequently, with ischemic stroke, or sinus thrombosis (Demopoulos and DeAngelis, 2002; Recht and Mrugala, 2003). Disseminated intravascular coagulation in particular contributes to the bleeding diathesis. Early in disseminated intravascular coagulation, fibrinolytic factors are consumed, which can lead to a paradoxical procoagulable state and to ischemic cerebrovascular episodes. Through the release of a procoagulant, especially with cell lysis, acute promyelocytic leukemia carries a particular risk for disseminated intravascular coagulation with mortality rates due to hemorrhagic complications as high as 30% (Kwaan et al., 2002). Evidence of disseminated intravascular coagulation includes schistocytes on the blood smear, elevated prothrombin time, decreased fibrinogen, increased fibrinogen degradation products, or the presence of D-dimer. The treatment for disseminated

Table 45.9

Inherited platelet disorders associated with cerebrovascular events

Syndrome	Gene (localization)	Inheritance	Clinical/laboratory features/pathogenesis
Wiskott–Aldrich syndrome (WAS)	WAS (Xp11)	X-L	Severe immunodeficiency, eczema. Small platelets, thrombocytopenia. Abnormal WAS protein
Amegakaryocytic thrombocytopenia (CAMT)	c-Mpl (1p34)	AR	Severe hypomegakaryocytic thrombocytopenia, progress to aplastic pancytopenia. Normal platelet size. Defect in the thrombopoietin (TPO)-receptor.
Thrombocytopenia with absent radii (TAR)	n.d.	AR	Severe neonatal thrombocytopenia, bilateral radial aplasia and/or other orthopedic abnormalities. Improving thrombocytopenia within 1st year of life. Defect signaling via the TPO receptor.
Bernard–Soulier syndrome (BSS)	GPIbα (17p13) GPIbβ (22q11) GPIX (3q21)	AD	Defect of GPIb-V-IX complex Homozygous subjects: defective ristocetin-induced platelet agglutination. Giant platelets. Heterozygous subjects: mild thrombocytopenia, normal ristocetin-induced platelet agglutination. Large platelets.
Sticky platelet syndrome (SPS)	n.d.	AD	Recurrent unexplained arterial/venous vascular occlusions. Platelet-hyperaggregability in platelet-rich plasma with adenosine diphosphate (ADP) and epinephrine (type I), epinephrine alone (type II), or ADP alone (type III).

X-L = X chromosomal linked; AR = autosomal recessive; AD = autosomal dominant; GP = platelet surface glycoprotein.
Adapted from Cines et al., 2004.

intravascular coagulation includes low-dose heparinoids, aggressive chemotherapy, and leukopheresis (Bick, 2002). The danger of major spontaneous bleeding in thrombocytopenia is minimal until the platelet count drops below 10×10^9/l. It is then considered as an independent risk factor for intracerebral hemorrhage and should be treated with platelet transfusion (Benjamin and Anderson, 2002; Demopoulos and DeAngelis, 2002; Recht and Mrugala, 2003). In patients with fulminant leukocytosis (blast crisis), particularly those with a leukocyte count over $200\,000 \times 10^6$/l, leukostasis, or blast cell thrombi within small arterioles can occur, resulting in tissue ischemia and hyperviscosity syndrome (Demopoulos and DeAngelis, 2002; Recht and Mrugala, 2003). Since the lungs and brain are predominantly affected, patients may experience shortness of breath, headache, visual and/or auditory disturbances, dizziness, or lethargy, progressing to an acute confusional state, focal neurologic deficits, or seizures. Acute lymphoid leukemia, acute myeloid leukemia, and acute promyelocytic leukemia, and chronic myelogenous leukemia (a myeloproliferative disorder with proliferation of granulocytes/neutrophils associated with chromosomal abnormality) have the highest incidence of leukostasis, chronic lymphocytic leukemia the lowest, even though WBC counts often exceed $200\,000 \times 10^6$/l. Hyperleukocytosis also produces vascular damage and massive hemorrhage through endothelial damage. Cerebral infarction is far less common in oncohematologic patients than hemorrhage and is mainly related to sinovenous thrombosis. Sinovenous thrombosis is frequently encountered in acute lymphoid leukemia and manifests clinically with headache, seizures, focal deficits, or altered consciousness. The pathogenic mechanisms contributing to venous occlusion are leukostasis, hypercoagulability (e.g., prothrombin G20210A mutation, factor V G1691A mutation), and use of certain chemotherapeutic agents, particularly L-asparaginase (Wermes et al., 1999; Demopoulos and DeAngelis, 2002; Recht and Mrugala, 2003; Santoro et al., 2005). Treatment consists of intravenous

heparin. Another cause of stroke is vasculitis, which arises in one of three settings: hairy cell leukemia, paraneoplastic vasculitis, or drug-induced vasculitis (e.g., hydroxyurea, vincristine, cytarabine, methotrexate, all-trans retinoic acid) (Paydas et al., 2000; Demopoulos and DeAngelis, 2002; Recht and Mrugala, 2003). Finally, ischemic strokes may also occur as a result of radiation-induced vascular damage.

45.2.3.1.2. Lymphomas

Clinical manifestations of lymphomas include weight loss, fever, or nightsweats (so-called B-symptoms), painless lymphadenopathy, splenomegaly, and (among others) coughing, and chest and abdominal discomfort. Laboratory anomalies include anemia, thrombocytopenia, elevated lactate dehydrogenase, aspartate amino transferase, alanine amino transferase, or alkaline phosphatase. The most common cerebrovascular complication of lymphomas consists of thrombosis of cortical veins and sinus (particularly of superior sagittal sinus), attributed to direct infiltration or compression of the sinus. Stroke related to disseminated intravascular coagulation or septic emboli have rarely been reported in lymphoma patients (Recht and Mrugala, 2003). Intravascular lymphomatosis is a rare large-cell lymphoproliferative disorder characterized by a widespread lymphoma proliferation within the lumen of medium-sized and small vessels, frequently presenting with skin and/or CNS manifestations. CNS involvement usually presents as subacute encephalopathy, dementia, seizures, or multifocal cerebrovascular events (Beristain and Azzarelli, 2002).

45.2.3.2. Plasma cell disorders

45.2.3.2.1. Multiple myeloma

Multiple myeloma is a malignant plasma-cell proliferative disease affecting mainly elderly patients (age 60–70 years). Symptoms are fatigue, bone pain, bleeding, infections, or renal impairment. It accounts for 1% of all malignancies and slightly more than 10% of all hematologic malignancies in Caucasians and 20% in African-Americans. The diagnosis is based on the presence of bone pain, anemia, and plasma-cell infiltrate in the bone marrow or within bone lesions (Kyle and Rajkumar, 2004). The outcome is highly variable (survival ranging from a few months to more than 10 years). Prognostic factors no longer solely rely on "classic" biological parameters (proliferative activity of plasma cells, beta-2-microglobulin (β2M), albumin, c-reactive protein, etc.), but cytogenetic and molecular markers (e.g., hyperdiploidy, translocation at 14q32, chromosome 13 delection) become more important (Harousseau et al., 2004; Kyle and Rajkumar, 2004). The therapeutic management of multiple myeloma for the last several decades has mainly involved regimens based on use of glucocorticoids and cytotoxic chemotherapeutics. Despite progress in delineating the activity of such regimens, multiple myeloma has remained an incurable disease, without substantial improvement in the median overall survival. Novel promising anti-multiple myeloma therapies include thalidomide and its more potent immunomodulatory derivatives, the first-in-class proteasome inhibitor bortezomib, and arsenic trioxide (As_2O_3) (Merlini et al., 2003).

45.2.3.2.2. Waldenström's macroglobulinemia

Waldenström's macroglobulinemia is an uncommon disease of the elderly, with a median age of 63 years (range 25–92), and a slight predominance of males over females. It accounts for approximately 2% of all hematologic malignancies, the incidence rate being higher among Caucasians (African descendants representing only 5% of patients) (Merlini et al., 2003). Onset of the disease is insidious, and patients may present with weakness, weight loss, pallor, fever, purpura or hemorrhagic manifestations, splenomegaly, hepatomegaly, and polyneuropathy. Anemia is the most common laboratory finding, and raised erythrocyte sedimentation rate is almost constantly observed. High-resolution electrophoresis combined with immunofixation of serum and urine are recommended for identification and characterization of the IgM monoclonal protein (Gertz et al., 2004). Age, sex, hemoglobin level, serum albumin, IgM level, and β2M predict outcome (Merlini et al., 2003). Therapeutic regimens include glucocorticoids and cytotoxic agents, and more recently thalidomide and monoclonal antibodies (Merlini et al., 2003; Gertz et al., 2004).

The above-mentioned disorders, as well as the related POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes), are associated with ischemic stroke and intracerebral hemorrhage (Kang et al., 2003; Recht and Mrugala, 2003; Drappatz and Batchelor, 2004; Gonthier and Bogousslavsky, 2004). Cerebrovascular complications generally result from hyperviscosity mostly due to hypergammaglobulinemia. The reasons for elevated viscosity are increased protein content and large molecular size, abnormal polymerization, and abnormal shape of immunoglobulin molecules. Other hematologic (elevated fibrinogen) and metabolic abnormalities (renal dysfunction) seen in patients with plasma cell dyscrasias also contribute to hyperviscosity (Mehta and Singhal, 2003). Monoclonal hypergammaglobulinemia resulting in hyperviscosity

syndrome is seen in multiple myeloma and particularly Waldenström's macroglobulinemia.

45.3. Coagulopathies

As depicted in Fig. 45.1, maintenance of hemostasis requires a complex interplay between procoagulant and anticoagulant mechanisms in the coagulation pathways. Increased levels of factors promoting coagulation, deficiencies of factors inhibiting coagulation, and decreased activity in the fibrinolytic pathway have all been implicated in thrombosis and can be associated with sinuvenous thrombosis and ischemic stroke (Table 45.2). Less commonly, congenital or acquired deficiencies of coagulation factors may lead to a bleeding diathesis (Tables 45.2 and 45.10), predisposing a patient to intracranial hemorrhage. Finally, various medical conditions, especially inflammatory processes and neoplastic disorders, interfere with hemostasis, often in complex ways, and contribute to pathological thrombosis and bleeding.

45.3.1. Bleeding disorders

45.3.1.1. Congenital bleeding disorders

45.3.1.1.1. Hemophilia A and B

Hemophilia A and B are rare x-linked recessive bleeding disorders caused by a deficiency of blood coagulation factor VIII (hemophilia A) or IX (hemophilia B), affecting about 1 in 10 000 and 1 in 30 000 males, respectively. At least 25% of patients with newly diagnosed hemophilia are sporadic (Mannucci and Tuddenham, 2001; Bolton-Maggs and Pasi, 2003). Bleeding tendency in hemophilia is related to the measured factor concentration and can be graded according to its severity as mild (5–40% of normal factor level), moderate (1–5% of average factor level), or severe (1% or less of average factor level) (White et al., 2001). In mild hemophilia, abnormal bleeding is usually associated with trauma, surgery, or tooth extraction, whereas in the severe form patients suffer from numerous bleedings from early age, particularly from spontaneous hemorrhage into muscles and joints (Mannucci and Tuddenham, 2001; Bolton-Maggs and Pasi, 2003). Intracranial hemorrhage is a leading cause of morbidity and mortality in patients with hemophilia, with a higher prevalence in younger patients (age <20 years in 75% of cases). Consistent with earlier reports in the literature, more recent studies quote a prevalence of intracerebral hemorrhage of 4–12%, and an incidence of about 2% per year (de Tezanos Pinto et al., 1992; Klinge et al., 1999; Nelson et al., 1999; Quinones-Hinojosa et al., 2003; Stieltjes et al., 2005). Spontaneous CNS bleeding is predominant in severe hemophilia. Thereby subarachnoidal, subdural, and intracerebral hemorrhage represent an equal proportion of the intracranial episodes. Even with improved therapy, the overall mortality rate is still high (35%), and over 50% of the patients suffer from long-term neurological sequelae (e.g., seizure disorders, motor impairment, neuropsychological deficits) (de Tezanos Pinto et al., 1992; Klinge et al., 1999; Nelson et al., 1999; Quinones-Hinojosa et al., 2003; Stieltjes et al., 2005). The definite diagnosis for patients with hemophilia relies on specific factor assays. Molecular techniques can be used to identify the genetic lesions that cause

Table 45.10

Inherited coagulation-factor deficiencies

Deficiency	Prevalence in 10^6 males	Gene on chromosome	Mode of inheritance
Fibrinogen	1	4	AR
Prothrombin	0.5	11	AR
Factor V	1	1	AR
Factor VII	2	13	AR
Factor VIII	100	X	X-L
Factor IX	24	X	X-L
Factor X	10	13	AR
Factor XI	1*	4	AR
Factor XIII	0.5	6 (subunit A) 1 (subunit B)	AR

Adapted from Mannucci and Tuddenham, 2001; Bolton-Maggs and Pasi, 2003.
AR = autosomal recessive; X-L = X chromosomal linked recessive.
*Higher in Ashkenazi Jews.

hemophilia and thus facilitate prevention of the disease through the identification of carriers and antenatal diagnosis (Mannucci and Tuddenham, 2001). There is currently no cure for hemophilia A or B. Current treatment for hemophilia-related bleeding episodes uses intravenous infusion of purified (risk of transmission of infectious agents) and recombinant (expensive, limited availability) factor proteins. In severe hemophilia A and B alloantibodies—so-called inhibitors—against infused factor VIII or IX occur with an estimated incidence of 33% and 3%, respectively. This complication has significant implications, as treatment response becomes uncertain, therefore increasing morbidity and direct medical costs and reducing life expectancy (Mannucci and Tuddenham, 2001; White et al., 2001; Bolton-Maggs and Pasi, 2003). Other important treatment issues are transfusion-transmitted infections and joint disease. The future goal of hemophilia treatment is correction of the molecular defect via gene therapy (Mannucci and Tuddenham, 2001; Bolton-Maggs and Pasi, 2003).

45.3.1.1.2. Von Willebrand disease

Von Willebrand disease is the most frequent inherited bleeding disorder, either in an autosomal dominant or recessive pattern. It is caused by quantitative (types 1 and 3) or qualitative (type 2) defects of von Willebrand factor, leading to abnormalities in platelet adhesion and aggregation, as well as to decreased factor VIII levels (Mannucci, 2001; Favaloro et al., 2004; Federici, 2004). Although a laboratory-defined decrease in the quantity of von Willebrand factor occurs in up to 1% of the population, probably less than 10% manifest symptoms of von Willebrand disease (Rodeghiero et al., 1987; Werner et al., 1993). Bleeding symptoms usually involve mucous membranes (e.g., epistaxis, menorrhagia, and gastrointestinal bleeding) and frequently occur after operative procedures (e.g., dental extraction). Mild von Willebrand disease forms are both under- and misdiagnosed, since factor VIII levels are usually only slightly reduced, whereas in type 3 (complete deficiency of von Willebrand factor) the severity of bleeding may resemble hemophilia with spontaneous hemarthroses or hematomas (Rodeghiero et al., 1987; Werner et al., 1993). There are a few anecdotic reports of intracranial hemorrhage associated with von Willebrand disease (Almaani and Awidi, 1986; Delangre et al., 1986). Diagnosis relies on laboratory evaluation (e.g., von Willebrand factor antigen level, von Willebrand factor activity (ristocetin cofactor, collagen binding), factor VIII activity (abnormal in only moderate/severe disease), and bleeding time) (Rick et al., 2003; Favaloro et al., 2004; Federici, 2004). The main therapeutic agents used to stop spontaneous bleeding and to prevent bleeding at the time of surgical procedures are desmopressin acetate (DDAVP—a non-transfusional agent) and plasma-derived factor VIII/ von Willebrand factor concentrates. Adjunctive therapies are platelet concentrates, synthetic fibrinolysis inhibitors, and topical preparations (Mannucci, 2001; Rick et al., 2003; Favaloro et al., 2004).

45.3.1.1.3. Congenital deficiencies of other coagulation factors

Congenital deficiencies of other coagulation factors account for only 15% of inherited hemophilias (Table 45.10). These are autosomal recessive conditions and therefore more prevalent in communities where consanguinity is common (e.g., factor XI deficiency, originally called hemophilia C, which is particularly common in Ashkenazi Jews) (Di Paola et al., 2001; Mannucci and Tuddenham, 2001; Bolton-Maggs and Pasi, 2003). The spectrum of symptoms in these conditions varies from a mild bleeding diathesis to severe and life-threatening hemorrhage. Some cases of intracranial hemorrhage have been reported (Peyvandi and Mannucci, 1999; Di Paola et al., 2001). The diagnosis depends on demonstration of decreased activity of the respective clotting factor. Due to the rarity of each of the individual factor deficiencies, purified factor concentrates are not as readily available (with the exception of recombinant factor VIIa—rFVIIa). Thus, treatment consists of the most purified blood product available that contains the missing factor (either purified concentrates, prothrombin complex concentrates, cryoprecipitate, or fresh frozen plasma) (Di Paola et al., 2001).

45.3.1.2. Acquired bleeding disorders

45.3.1.2.1. Acquired hemophilia

Acquired hemophilia is a rare, but often serious coagulopathy caused by autoantibodies against a coagulation factor, most frequently factor VIII. Other autoantibodies have been described against factors V, VII, XI and, rarely, factor XIII, von Willebrand factor and prothrombin. The overall annual incidence is estimated to be about 0.2–1 per million. Although the etiology of this disorder often remains obscure (idiopathic acquired hemophilia), about 50% of cases are associated with underlying malignancies, post-partum period, drug administration or autoimmune diseases such as rheumatoid arthritis or systemic lupus erythematosus (Boggio and Green, 2001; Watson et al., 2001; Delgado et al., 2003; Holme et al., 2005). Acquired hemophilia presents with bleeding into the skin, muscles, gastrointestinal and genitourinary tracts, and

other sites. Intracranial hemorrhage has rarely been reported (Delmer et al., 1989; Quinones-Hinojosa et al., 2003; Holme et al., 2005). The mortality rate is high (8–22%) and severe life-threatening bleeds have been reported to occur in about 85% of patients. Spontaneous remission is often seen for the pregnancy and post-partum-related acquired hemophilia (after an average of 30 months). The selection of therapeutic concentrates for the management of acute bleeding is related to the titer of the inhibitor (measured in Bethesda units). With high inhibitor titer, bleeding usually responds only to porcine factor VIII, recombinant factor VIIa, or activated prothrombin complex concentrates (Boggio and Green, 2001; Delgado et al., 2003; Holme et al., 2005). In 50% of patients, corticosteroids lead to disappearance of the autoantibody. Alternatively, other immunosuppressants (e.g., cyclophosphamide, azathioprine, cyclosporine) are also effective. High-dose intravenous immunoglobulin, plasmapheresis or immunosorbent columns transiently decrease inhibitor titers and enable control of bleeding. New approaches, as methods to establish tolerance, are in development (Boggio and Green, 2001; Delgado et al., 2003).

45.3.1.2.2. Iatrogenic bleeding disorders

Iatrogenic coagulopathies are one of the most prevalent category of acquired bleeding disorders and result from antiplatelet agents, heparins, coumadins, fibrinolytics, or, less frequently, from other drugs (e.g., nonsteroidal anti-inflammatories) (Watson et al., 2001; Quinones-Hinojosa et al., 2003). They may also be associated with intracranial hemorrhage, and are therefore discussed elsewhere.

45.3.2. Thrombophilia

45.3.2.1. Coagulation inhibitors

45.3.2.1.1. Protein C deficiency

Protein C is a vitamin K dependent anticoagulant, which circulates as a two-chain zymogen. It is converted into an active protease (activated protein C) by thrombin, after binding to endothelial surfaces through thrombomodulin. Activated protein C, in conjunction with protein S, inactivates clotting factors Va and VIIIa (Fig. 45.1), promotes fibrinolysis and accelerates clot lysis. Deficiency of protein C usually results from autosomal dominant mutation of the encoding gene on chromosome 2, but dysfunctional protein C has also been reported. Deficiency of protein C can be recognized by low concentration of the protein or by low functional activity using functional and immunological assays (Markus and Hambley, 1998; Dahlback, 2005; Weber and Busch, 2005). Thus, familial protein C deficiency can be classified into two types (type I characterized by parallel reductions of functional and immunoreactive protein C, in type II the functional level being substantially lower than that of the antigen) (Haemostasis and Thrombosis Task Force; British Committee for Standards in Haematology, 2001). The prevalence of heritable protein C deficiency in the general population is approximately 0.2–0.4% (Table 45.11), but symptomatic heterozygotes are far less common (Miletich et al., 1987; Gladson et al., 1988; De Stefano et al., 2002). They have an five- to eight-fold higher risk for venous thrombosis (also sinovenous thrombosis) compared to healthy subjects, whereas reports regarding ischemic cerebral infarction are conflicting (Coull and Goodnight, 1990; Hart and Kanter, 1990; Tatlisumak and Fisher, 1996; Markus and Hambley, 1998; Green, 2003; Moster, 2003; Weber and Busch, 2005). Some small case series have suggested that protein C deficiency may be associated with an increased risk of non-hemorrhagic stroke, but larger studies have not supported these findings in adults, whereas in children a possible causal relation cannot be completely excluded (Douay et al., 1998; Margaglione et al., 1999; Hankey et al., 2001; Olah et al., 2001; Strater et al., 2002; Haywood et al., 2005). Determining the association of protein C deficiency and stroke is difficult, since protein C concentrations in asymptomatic deficient people overlap with those seen in patients with recurrent thrombo-embolism. Furthermore, in the acute stage of stroke, low plasma levels of protein C rather reflect consumption and may return to normal within a few months. Also, various other conditions are associated with decreased protein C levels (Table 45.12). Therefore, a confirmatory measurement 2–3 months later is needed for the diagnosis of protein C deficiency (Tatlisumak and Fisher, 1996; Markus and Hambley, 1998; Haemostasis and Thrombosis Task Force; British Committee for Standards in Haematology, 2001; Weber and Busch, 2005). Although no prospective study exists, it is generally recommended that patients with primary protein C deficiency and stroke should be treated with oral anticoagulants, preferably overlapped by adequate heparinization to prevent the rare complication of skin necrosis. Whether these should be continued for life remains uncertain (Haemostasis and Thrombosis Task Force; British Committee for Standards in Haematology, 2001).

45.3.2.1.2. Protein S deficiency

Protein S is another vitamin K dependent plasma glycoprotein, synthesized primarily in the liver and encoded on chromosome 3. In plasma about two-thirds

Table 45.11

Prevalence of inherited thrombophilia in ischemic stroke

Thrombophilia	Pattern of inheritance: %	Type of assay	Confirmation required	Prevalence in Caucasian population	Prevalence in ischemic stroke	Prevalence in ischemic stroke <50 years
PC deficiency	AD	Functional	Yes, after 3 months	0.2–0.4%	<0.5%	0–5.3%
PS deficiency	AD	Functional	Yes, after 3 months	0.03–0.13%	<0.2%	0–6.1%
AT deficiency	AD	Functional	Yes, after 3 months	0.02–0.2%	0.02–0.2%	0%
FV Leiden	AD	APCR screen	Yes, FV Leiden genotyping	4.8–5.0%	4.6–7.0%	5.3–11.0%
PT G20210A	AD	PT genotyping	No	0.7–4.0%	3.7–4.5%	2.5–7.6%

PC = protein C; PS = protein S; AT = antithrombin; FV Leiden = factor V Leiden mutation; PT G20210A = prothrombin gene mutation; APCR = activated protein C resistance; AD = autosomal dominant.
Adapted from Bushnell and Goldstein, 2002b; Weber and Busch, 2005.

Table 45.12

Several causes of acquired protein C, protein S or antithrombin III deficiency

Extensive thrombosis; stroke
Nephrotic syndrome
Severe liver disease
Disseminated intravascular coagulation
Postoperative period
Treatment with warfarin; heparin
Hormonal contraception; pregnancy
Vitamin K deficiency

are bound to a C4b-binding protein (C4bBP). Only the remaining free form is active, serving as a cofactor for activated protein C. Therefore for full assessment both total and active or "free" protein S need to be measured. Three main types of assay are available: for functional protein S, and for total or free immunoreactive protein S. Three types of protein S deficiency are described (type I, a quantitative defect caused by genetic abnormalities which result in the reduced production of structurally normal protein; type II, a functional defect; type III, where free protein S antigen is reduced, although the total protein S antigen level is normal) (Hart and Kanter, 1990; Tatlisumak and Fisher, 1996; Markus and Hambley, 1998; Haemostasis and Thrombosis Task Force; British Committee for Standards in Haematology, 2001; Green, 2003; Weber and Busch, 2005). With a prevalence of less than 0.2% in a Caucasian population hereditary protein S deficiency is rare (Table 45.11), but still responsible for 5% of unexplained venous thrombotic events (Gladson et al., 1988; Tait et al., 1994; Esmon et al., 1999; Weber and Busch, 2005). As is the case for protein C, it is difficult to ascertain the possible association between protein S deficiency and stroke. Free protein S levels are decreased in acute stroke and altered by various factors, especially estrogen-containing oral contraceptives or hormone replacement therapy (Table 45.12). Thus, the numerous anecdotal reports, small series and case-control studies have not convincingly established an etiologic role of protein S in ischemic cerebrovascular incidents (Green et al., 1992; Mayer et al., 1993; Adams et al., 1995; Douay et al., 1998; Margaglione et al., 1999; Olah et al., 2001). The recommendations are the same as for protein C deficiency: follow up concentrations after 3 months to confirm protein S deficiency, and in the presence of persistent protein S deficiency in stroke to start anticoagulation treatment (Markus and Hambley, 1998; Haemostasis and Thrombosis Task Force; British Committee for Standards in Haematology, 2001; Weber and Busch, 2005).

45.3.2.1.3. Protein Z and protein Z-dependent protease inhibitor

Protein Z-dependent protease inhibitor is a serpin that functions as a natural anticoagulant, inhibiting the activated coagulation factors X and XI by two separate mechanisms (Han et al., 2000). The inhibition of factor X requires calcium and phospholipids and is enhanced approximately 1000-fold in the presence of the cofactor, protein Z. Protein Z is a vitamin K-dependent plasma glycoprotein, synthesized by the liver (Broze, 2001). Inhibition of factor XIa by protein Z-dependent

protease inhibitor does not require protein Z, calcium ions, or phospholipids, but is enhanced by heparin (Han et al., 2000). Deficiency of human protein Z has been reported to be associated with thrombotic events of the coronary arterial bed and placental circulation, but not of the deep venous system (Gris et al., 2002; Fedi et al., 2003; Al-Shanqeeti et al., 2005). One study suggests an association between protein Z-dependent protease inhibitor deficiency and venous thrombosis (Water et al., 2004). Clinical studies have implicated protein Z deficiency as a risk factor in ischemic stroke (Vasse et al., 2001; Heeb et al., 2002). The results conflict with those of others who either found no association or an increased risk of stroke among patients with elevated concentrations of protein Z in the blood (Kobelt et al., 2001; McQuillan et al., 2003; Staton et al., 2005). To date, no definite conclusion on the role of protein Z/ protein Z-dependent protease inhibitor in ischemic stroke can be drawn.

45.3.2.1.4. Antithrombin deficiency

The glycoprotein antithrombin—previously known as antithrombin III—is synthesized by hepatocytes and endothelial cells. Antithrombin inhibits thrombin, but also other coagulation factors (IXa, Xa, XIa, XIIa and tissue factor-bound factor VIIa), and kallikrein. Heparins markedly accelerate the rate of complex formation between antithrombin and the serine proteases. Antithrombin deficiency can be congenital or acquired (Table 45.12). Inherited antithrombin deficiency is an autosomal dominant trait due to mutations of the gene on chromosome 1. Two major types are recognized (type I characterized by a quantitative reduction of functionally normal antithrombin, type II by the production of a qualitatively abnormal protein). For type II, dysfunctional antithrombin molecules with mutations affecting either the serine protease binding site or the heparin binding site (or both) are recognized. The distinction between the subtypes of antithrombin deficiency is of clinical relevance as the incidence of thrombosis varies (Hart and Kanter, 1990; Tatlisumak and Fisher, 1996; Markus and Hambley, 1998; Haemostasis and Thrombosis Task Force; British Committee for Standards in Haematology, 2001). The prevalence of hereditary antithrombin deficiency in the general population is of the order of 0.02–0.2% (Table 45.11) (Tait et al., 1994; De Stefano et al., 2002; Weber and Busch, 2005). Hereditary antithrombin deficiency has been associated with a >25-fold elevated risk of developing venous thrombosis (including cerebral veins and sinus), whereas arterial occlusion has rarely been reported (Markus and Hambley, 1998; Rosendaal, 1999; Haemostasis and Thrombosis Task Force; British Committee for Standards in Haematology, 2001; De Stefano et al., 2002).

With regard to the larger studies, the evidence linking hereditary antithrombin deficiency with ischemic stroke is weak (Green et al., 1992; Adams et al., 1995; Margaglione et al., 1999; Hankey et al., 2001; Olah et al., 2001; Moster, 2003; Haywood et al., 2005). Antithrombin deficiency can be acquired, or stroke may underlay with other vascular risk factors. For confirmed hereditary antithrombin deficiency treatment with heparin alone is not sufficient, since heparin requires antithrombin to exert its anticoagulant action. Long-term warfarin therapy is recommended. Depending on the severity of the thrombo-embolic complication or number of recurrences, a lifelong treatment may be reasonable (Tatlisumak and Fisher, 1996; Markus and Hambley, 1998; Haemostasis and Thrombosis Task Force; British Committee for Standards in Haematology, 2001).

45.3.2.1.5. Heparin cofactor II

Heparin cofactor II is a serine protease inhibitor (serpin) synthesized by the liver that inhibits thrombin but has no activity against other proteases involved in coagulation or fibrinolysis. This inhibitory function is enhanced more than 1000-fold in the presence of heparin, heparan sulfate, or dermatan sulfate (Tollefsen, 2002). Hereditary heparin cofactor II deficiency has been described, caused by a mutation of the gene on chromosome 22, and inherited as an autosomal dominant trait. But heparin cofactor II deficiency seems not to be related to increased risk of thrombosis or stroke (Villa et al., 1999; Tollefsen, 2002; Corral et al., 2004).

45.3.2.2. Coagulation factors

45.3.2.2.1. Activated protein C resistance, factor V Leiden mutation

Activated protein C resistance is defined as an impaired anticoagulant effect of activated protein C, when added to the patient's plasma in vitro (Dahlback et al., 1993). In 90–95% of cases, activated protein C resistance is due to a point mutation (base exchange) in the gene of coagulation factor V on chromosome 1 (G1691A), the "factor V Leiden" mutation (Bertina et al., 1994). This results in a modification of factor Va at the cleavage site (Arg506Gln) of activated protein C, so that factor Va cannot be inactivated properly by activated protein C (Greengard et al., 1994). Other causes of activated protein C resistance include the factor V receptor 2 haplotype and rare mutations affecting factor V at a different activated protein C cleavage site (Williamson et al., 1998; Vos, 2006). Changes in hemostasis cause acquired activated protein C resistance (e.g., elevated factor VIII), but activated protein C resistance increases also with age, on hormonal

replacement therapy, or during pregnancy. The most commonly used screening test systems for diagnosis of activated protein C resistance are based on the original or modified activated partial thromboplastin time ratio (predilution of patient plasma with factor V-depleted plasma), but direct detection of the factor V Leiden mutation is also possible by polymerase chain reaction (Haemostasis and Thrombosis Task Force; British Committee for Standards in Haematology, 2001). Factor V Leiden is the most frequent inherited prothrombotic state in the Caucasian population with a prevalence of about 5–6% (Table 45.11). It is less common in Africans, and rare in Asians (Rees et al., 1995; Ridker et al., 1997; Larsen et al., 1998; De Stefano et al., 2002). Whereas numerous studies have established factor V Leiden as the most frequent hereditary thrombophilic disorder predisposing heterozygous carriers to a three- to eight-fold increased risk of venous thrombosis (Ridker et al., 1995; Rosendaal, 1999; De Stefano et al., 2002), the role of factor V Leiden in arterial thrombosis remains controversial. Due to the observed trend of decreasing prevalence of factor V Leiden with advancing age some authors suggested factor V Leiden mutation to be a risk factor for ischemic stroke especially in the age groups of less than 40 years old and in children. But larger case-control studies have failed to confirm a significant association between activated protein C resistance or the factor V Leiden mutation and stroke (Catto et al., 1995; Ridker et al., 1995; Margaglione et al., 1999; Nowak-Gottl et al., 1999; Bushnell and Goldstein, 2000; Hankey et al., 2001; Lopaciuk et al., 2001; Juul et al., 2002; Green, 2003; Moster, 2003; Haywood et al., 2005; Weber and Busch, 2005). In view of the frequency of asymptomatic heterozygotes for the factor V Leiden mutation in the normal population and the lack of controlled studies the optimal treatment of stroke patients with the factor V Leiden mutation is uncertain. However, in young patients with no other obvious cause of stroke anticoagulation with warfarin for at least 6 months (in case of life-threatening events, lifelong) seems a reasonable approach (Haemostasis and Thrombosis Task Force; British Committee for Standards in Haematology, 2001).

45.3.2.2.2. Prothrombin gene mutation

The G20210A mutation (G to A transition at nucleotide 20210) in the prothrombin (factor II) gene is the second most common hereditary cause of venous thrombosis. The prothrombin mutation is associated with elevated plasma prothrombin levels and an increased risk of venous thrombosis (Poort et al., 1996). The prevalence in Europe is around 2% in the healthy population and 6% in unselected patients with a first thrombosis. It is rarely found in Africans and Asians (Poort et al., 1996; Haemostasis and Thrombosis Task Force; British Committee for Standards in Haematology, 2001; De Stefano et al., 2002; Green, 2003; Weber and Busch, 2005). The risk of venous thrombosis in heterozygous carriers of the G20210A allele is estimated to be around three times that in non-carriers. An association between the prothrombin mutation and cerebral venous thrombosis has been described, especially for women using oral contraceptives (Martinelli et al., 1998). Most studies showed insignificant or borderline significant associations of prothrombin mutation and stroke (De Stefano et al., 1998; Margaglione et al., 1999; Bushnell and Goldstein, 2000; Hankey et al., 2001; Lopaciuk et al., 2001; Wu and Tsongalis, 2001; Austin et al., 2002; Strater et al., 2002; Green, 2003; Moster, 2003; Haywood et al., 2005; Weber and Busch, 2005). As for the factor V Leiden mutation, the empiric treatment recommendation is anticoagulation therapy.

45.3.2.2.3. Elevated coagulation factors

It is still uncertain how far elevated levels of coagulation factors predispose to arterial thrombo-embolic events. Coagulation factors circulate as zymogens (inactive form) in relatively high concentrations. Thus, increased levels of coagulation factors do not necessarily imply a hypercoaguable state. Elevated fibrinogen, coagulation factor V, factor VIII, and von Willebrand factor have been associated with ischemic stroke. This literature mostly antedates testing for protein C/S deficiency or factor V Leiden/prothrombin mutation (for a review see Catto and Grant, 1995). At present, elevated fibrinogen has been confirmed as a risk factor for ischemic stroke by large prospective studies, whereas no definite conclusion can be drawn on the association of other coagulation factors and the risk of ischemic stroke (Qizilbash et al., 1997; Smith et al., 1997; Folsom et al., 1999; Kario et al., 2000; Demarmels Biasiutti et al., 2003; Smith et al., 2005).

45.3.2.3. Defects of fibrinolysis

45.3.2.3.1. Plasminogen deficiency

Hereditary plasminogen deficiency is a rare autosomal dominant disorder, qualitative and quantitative, predisposing to venous thrombosis. There are only a handful of case reports associating low functional levels of plasminogen activity in young people with cortical venous thrombosis or stroke (Dolan et al., 1988; Furlan et al., 1991; Nagayama et al., 1993).

45.3.2.3.2. Dysfibrinogenemia

About 250 cases of hereditary dysfibrinogenemia have been reported, characterized by normal or only mildly

decreased concentrations of abnormal fibrinogen molecules that are resistant to cleavage by plasmin. Most heterozygotes with this autosomal dominant trait are asymptomatic and found coincidentally due to a prolonged prothrombin time or prolonged thrombin time (Haverkate and Samama, 1995). However, in about 20% there is an increased tendency to arteriovenous thromboembolism and in 25% to bleeding. The prevalence of fibrinogen abnormalities in patients with venous thrombosis is low (0.8%), but a high incidence of post-partum thrombosis and an increased risk of pregnancy loss have been reported (Haverkate and Samama, 1995). Rarely stroke has been reported in patients with dysfibrinogenemia (Quattrone et al., 1983; Lounes et al., 2000).

45.3.2.3.3. Plasminogen activator inhibitor 1

Elevated plasminogen activator inhibitor-1 (PAI-1) levels have been associated with impaired fibrinolytic activity and thus with arteriovenous thromboembolism including ischemic stroke (Margaglione et al., 1994; Zunker et al., 1999; Smith et al., 2005). PAI-1 plasma levels show a great (also circadian) variability and have a genetic influence. The PAI-1 promoter 4G/4G genotype, however, is not associated with ischemic stroke (Endler et al., 2000; Nowak-Gottl et al., 2001; Austin et al., 2002).

45.3.2.3.4. Tissue plasminogen activator

Elevated tissue plasminogen activator (tPA) concentrations are related to increased endogenous fibrinolysis, but have also been associated with an increased risk of arterial thrombosis, as myocardial infarction and stroke (Ridker et al., 1994; Smith et al., 1997). A recent prospective study did not confirm these findings (Smith et al., 2005). Since the tPA gene polymorphism influences transcriptional activity, a higher prevalence of a certain tPA allele among ischemic stroke cases would be expected, but so far study results diverge (Austin et al., 2002; Jood et al., 2005).

45.3.2.3.5. Factor XII (Hageman factor) deficiency

Besides the activation of blood coagulation, factor XII (Hageman factor) is also involved in the stimulation of endogenous fibrinolysis, in kinin production, and in complement activation (Dahlback, 2005). Despite previous reports, factor XII deficiency is not associated with bleeding problems, nor does it seem to be related to the occurrence of venous or arterial thrombosis. Occasionally reported sinovenous thrombosis or ischemic strokes are more likely due to other underlying medical conditions or coagulation abnormalities (Tatlisumak and Fisher, 1996; Zeerleder et al., 1999; Girolami et al., 2004).

45.3.3. Disseminated intravascular coagulation

Disseminated intravascular coagulation is an acquired syndrome characterized by hypercoagulable state, hemorrhagic symptoms, and multiple organ failure (Taylor et al., 2001). The occurrence of microvascular thrombosis as a consequence of widespread systemic activation of coagulation with intravascular deposition of fibrin contributes to end-organ damage, whereas the simultaneous consumption of coagulation factors and platelets results in bleeding (Levi and Ten Cate, 1999; Bick, 2002; Toh and Dennis, 2003; Levi, 2004). A variety of clinical conditions may cause disseminated intravascular coagulation, whereby sepsis and trauma are the most common (Table 45.13) (Toh and Dennis, 2003; Levi, 2004; Barret and Gomez, 2005). Pathogenetic pathways that play a role in the development of disseminated intravascular coagulation include tissue factor-dependent activation of coagulation, defective physiological anticoagulant pathways (such as the antithrombin and protein C systems), and impaired fibrinolysis due to elevated

Table 45.13

Clinical conditions associated with disseminated intravascular coagulation

Condition	Causes
Sepsis/severe infection	Potentially any micro-organism
Trauma	Head trauma Crush injuries Fat embolism Burn injury
Malignancy	Solid tumors Hematological malignancies (e.g., myeloid or lymphoid neoplasms)
Obstetrics/gynecology	Amniotic fluid embolism Placental abruption Eclampsia Abortion
Vascular abnormalities	Giant hemangiomas (Kasabach–Merritt syndrome) Large vascular aneurysms
Organ damage	Severe hepatic failure Severe pancreatitis
Severe toxic/ immunological reactions	Snake bites Transfusion reactions Transplant rejection
Various	Prosthetic devices (e.g., aortic balloon assist device)

Adapted from Toh and Dennis, 2003; Levi, 2004.

levels of plasminogen activator inhibitor type 1. Additionally, a distinct role for enhanced inflammatory activity and in particular for activated neutrophils has also been suggested. Thereby, inflammatory cytokines promote coagulation by leading to intravascular tissue factor release, eliciting the expression of leukocyte adhesion molecules on the intravascular cell surfaces, and downregulating the fibrinolytic and protein C anticoagulant pathways. Thrombin, in turn, can promote inflammatory responses (Esmon et al., 1999; van der Poll et al., 2001; Levi, 2004).

Disseminated intravascular coagulation can cause ischemic and hemorrhagic stroke, or rarely sinovenous thrombosis (Schwartzman and Hill, 1982; Winkelman and Galloway, 1992; Quinones-Hinojosa et al., 2003; Rogers, 2003). Small- and large-vessel occlusion, intracranial hemorrhage, and subarachnoidal hemorrhage have been described. The lesions are usually small and cause encephalopathy, coma, or seizures, rather than focal neurological deficits (Schwartzman and Hill, 1982). Hemorrhage in disseminated intravascular coagulation is rarely restricted to the brain and therefore a manifestation of systemic bleeding, as purpura, petechiae, or massive hemorrhage, is usually present. The clinical and laboratory diagnosis of disseminated intravascular coagulation remains difficult, since routinely available tests do not specifically assess ongoing thrombin generation. The classically characterized findings are prolonged clotting times (e.g., prothrombin time, activated partial thromboplastin time), elevated products of fibrin breakdown (e.g., fibrin monomeres, D-dimer), low platelet counts, and low fibrinogen. Results within the normal range do not exclude important consumptive coagulopathy. A proposed algorithm using a combination of widely available tests, however, may be helpful in making the diagnosis of disseminated intravascular coagulation (Table 45.14), as well as newer, more specific assays linking inflammation and coagulation (e.g., protein C) (Taylor et al., 2001; Liaw et al., 2003; Levi, 2004). Appropriate treatment and supportive care are essential in the management of disseminated intravascular coagulation, but are often not sufficient. Although it has not been proven by randomized controlled trials, replacement treatment with plasma or platelets is used for patients with either active bleeding or at risk of bleeding. Heparin is the treatment of choice for patients with clinically overt thrombo-embolism or extensive fibrin deposition (Toh and Dennis, 2003; Levi, 2004). Novel therapeutic strategies are based on current insights into the pathogenesis of disseminated intravascular coagulation, and include anticoagulant strategies (e.g., directed at tissue factor) and strategies to restore physiological anticoagulant pathways (such as activated protein C concentration) (Abraham et al., 2003; Liaw et al., 2003).

Table 45.14

Diagnostic algorithm for disseminated intravascular coagulation. In a patient with an underlying disorder known to be associated with overt DIC score the results of the following global coagulation tests.

Platelet count	$>100 \times 10^9$/l	= 0
	$50–100 \times 10^9$/l	= 1
	$<50 \times 10^9$/l	= 2
Prolonged prothrombin time	<3 s	= 0
	3–6 s	= 1
	>6 s	= 2
Fibrin-related marker*	No increase	= 0
	Moderate increase	= 1
	Strong increase	= 2
Fibrinogen level	>1.0 g/l	= 0
	<1.0 g/l	= 1

A score ≥5 is compatible with overt DIC (repeat score daily).
A score <5 is not affirmative for DIC (repeat score next 1–2 days).
*e.g., soluble fibrin monomers/fibrin degradation products.
Adapted from Taylor et al., 2001.

45.4. Antiphospholipid syndrome

45.4.1. Overview

Antiphospholipid syndrome is an acquired disorder characterized by recurrent thrombosis or spontaneous abortions, and the persistent presence of antiphospholipid antibodies (Hughes et al., 1986; Harris et al., 1988; Feldmann and Levine, 1995; Levine et al., 2002; Gezer, 2003).

Antiphospholipid antibodies are a heterogeneous group of circulating polyclonal (IgM, IgG, IgA or mixed isotypes) immunoglobulins directed toward phospholipid-protein complexes. The two most relevant antiphospholipid antibodies are anticardiolipin antibodies and the lupus anticoagulant (Triplett, 1995). Lupus anticoagulant acts as a coagulation inhibitor not through interference with a specific coagulation factor but by interactions with phospholipid dependent steps of blood coagulation. It slows the rate of thrombin generation and is therefore detected in coagulation assays, as listed in Table 45.15 (Brandt et al., 1995; Triplett, 1995; Greaves, 1999). By contrast, immunoassays are used to reveal anticardiolipin antibodies (Triplett, 1995; Greaves, 1999; Wilson et al., 1999).

Table 45.15

Laboratory detection of antiphospholipid antibodies

Coagulation assays		
	Lupus anticoagulant antibodies	
		For diagnosis of LA the following steps are required: 1. Prolonged phospholipids-dependent coagulation in at least one screening test (studies: aPTT, PT, KCT, dRVVT, TTI, Staclot-LA and others) 2. Failure to correct with mixing studies 3. Demonstration of phospholipids specificity 4. Exclusion of other coagulopathy
Immunological assays		
	Cardiolipin antibodies	
		β_2-glycoprotein I antibodies Solid-phase immunoassay on coated plates of the specific phospholipids or phospholipid-binding proteins (usually ELISA)

aPTT = activated partial thromboplastin time; PT = prothrombin time; KCT = kaolin clotting time; dRVVT = dilute Russell viper venom time; TTI = tissue thromboplastin inhibition test; Staclot-LA = hexagonal (II) phase phospholipid assay; ELISA = enzyme-linked immunoabsorbent assay.

Low-titer antiphospholipid antibodies are found in 1–5% of asymptomatic young healthy control subjects, with a proportion of about 2% of persistently elevated antibody titers over several months (Bick, 2001). However, the prevalence of antiphospholipid antibodies also increases with age and coexistent chronic diseases, thus in several studies anticardiolipin antibodies were detected in up to 52% of elderly individuals (Manoussakis et al., 1987; Fields et al., 1989; Schved et al., 1994; Vila et al., 1994). Transient elevations of antiphospholipid for instance are frequently observed after a variety of infections and tissue trauma and may also be induced by several drugs (Table 45.16) (Greaves, 1999; Levine et al., 2002). Hence, most of them do not show any clinical significance.

In contrast, antiphospholipid syndrome currently represents the most common identifiable cause of acquired thrombophilia and is considered to be an established risk factor of venous as well as arterial thrombosis (Bick and Baker, 1994). Deep venous thrombosis, especially of the legs, is the most common clinical manifestation of antiphospholipid syndrome, and ischemic stroke the most frequent arterial occlusive event (Asherson et al., 1989; Vianna et al., 1994; Levine et al., 2002). However, occlusion of virtual every peripheral and visceral artery (e.g., myocardial infarction) may occur, whereas bleeding complications seems to be extraordinarily rare (Levine et al., 2002; Gezer, 2003). Obstetric problems are common manifestations of antiphospholipid syndrome and include spontaneous abortions, preterm labor, low birth weight, pre-eclampsia and stillbirth (Lockwood and Rand, 1994). Furthermore, left-sided cardiac valvular abnormalities are frequently recognized (Vianna et al., 1994; Turiel et al., 2005). Livedo reticularis is a rarer, but distinct manifestation of antiphospholipid syndrome, whereas some others are possibly, but not unequivocally associated with antiphospholipid antibodies (e.g., migraine-like events, chorea, or pulmonary hypertension) (Levine et al., 2002; Gezer, 2003). Rarely, patients with antiphospholipid syndrome develop fulminant multiple organ failure, which is called "catastrophic" antiphospholipid syndrome. Laboratory features include prolonged activated partial thromboplastin time, thrombocytopenia, false-positive venereal disease research laboratory test, and a usually mild-to-moderate positive antinuclear antibody test (Asherson et al., 1989; Vianna et al., 1994; Levine et al., 2002; Gezer, 2003). Possible clinical and laboratory features are summarized in Table 45.17.

Antiphospholipid syndrome can occur within the context of several, mainly autoimmune disorders, and is then called secondary antiphospholipid syndrome (Table 45.16). In the absence of any recognizable disease it is referred to as primary antiphospholipid syndrome (Asherson et al., 1989). The syndrome occurs in young to middle-aged adults with

an age of onset of generally less than 50 years and a female predilection (Terashi et al., 2005). There is no defined racial predominance for primary antiphospholipid syndrome, although a higher prevalence of systemic lupus erythematosus occurs for instance in African-Americans.

Table 45.16

Underlying medical conditions associated with antiphospholipid antibodies

Primary antiphospholipid syndrome	
Rheumatic and connective tissue disorders (secondary antiphospholipid syndrome)	
	Systemic lupus erythematodes (SLE)
	Rheumatoid arthritis
	Systemic sclerosis
	Sjögren's syndrome
	Beçet's disease etc.
Infections	
	Viral (e.g., HIV, hepatitis C)
	Bacterial (e.g., syphilis)
	Parasitic (e.g., malaria)
Medications	
	Phenytoin
	Quinidine
	Phenothiazine
	Hydralazine
	Procainamide
	Alpha-interferon
Miscellaneous	
	Lymphoproliferative disorders
	Sickle-cell disease
	Myocardial infarction
	Cocaine abuse
	Guillain–Barré syndrome

45.4.2. Antiphospholipid syndrome and stroke

Arterial thrombosis in antiphospholipid syndrome tends to involve primarily cerebral and ocular vessels. In about 20% of patients with antiphospholipid syndrome, stroke or TIA represent the first manifestation of the disease. This association of antiphospholipid antibodies with ischemic stroke as the most common arterial thrombotic event has been demonstrated by numerous case-control and prospective studies (Asherson et al., 1989; Coull and Goodnight, 1990; Kushner, 1990; Montalban et al., 1991; APASS—Antiphospholipid Antibodies in Stroke Study Group, 1993a; Feldmann and Levine, 1995; Brey et al., 2001), albeit not consistently (Ginsburg et al., 1992; Muir et al., 1994).

Depending on study design and population, stroke patients tested positive for antiphospholipid antibodies, lupus anticoagulant, or both in 6.8–41% (Montalban et al., 1991; APASS, 1993a, 2004). Therefore, antiphospholipd antibodies have been implicated as an independent risk factor for a first ischemic stroke, raising the relative risk by about 2.2 to 2.3 (APASS, 1993a; Brey et al., 2001). The issue of antiphospholipid antibodies in predicting recurrent ischemic stroke is much more controsversial (APASS, 1993a, 1997; Brey et al., 2001; Heinzlef et al., 2001; APASS, 2004). The recurrence rate was thought to be high among patients with ischemic stroke and positive testing for antiphospholipid antibodies, and reports suggested an annual risk up to 10% (APASS, 1993a). However, in the most recent prospective cohort of the Antiphospholipid Antibodies and Stroke Study (APASS) within the

Table 45.17

Clinical and laboratory features associated with antiphospholipid syndrome and antiphospholipid antibodies

A Clinical					B Laboratory
Venous thrombosis	Arterial thrombosis	Heart disease	Other	Neurological	
Deep vein	Cerebral	Verrucous endocarditis	Miscarriages	Chorea	Prolonged aPTT
Cerebral	Pulmonary	Myxomatous mitral valve degeneration	Livedo reticularis	Migraine headache	False-positive VDRL
Retinal	Myocardial		Acalculous cholecystitis	Seizures	Thrombocytopenia
Hepatic	Extremities	Pulmonary hypertension			Positive ANA
Portal	Ocular	Intracardiac thrombi			Reduced complement C4
Renal		Dermal			Hemolytic anemia
		Mesenteric			

aPTT = activated thromboplastin time; VDRL = veneral disease research laboratory test; ANA = antinuclear antibodies.

Warfarin versus Aspirin Recurrent Stroke Study (WARSS) (Mohr et al., 2001), immunoreactivity to antiphospholipid antibodies did not influence the risk for subsequent vascular occlusive events over 2 years. Only a small subgroup of patients who tested positive for both anticardiolipin and lupus antibodies tended to be at greater risk of death or thrombo-occlusive event during the 48 months of follow-up (APASS, 2004). The same seems to be true for the pediatric patients group (Lanthier et al., 2004).

Ischemic stroke are usually moderately sized and involve the territory of small to large branches of the middle cerebral artery. Vasculitis rarely occurs with antiphospholipid syndrome (APASS, 1990). Angiography is normal in about one-third of cases or demonstrates the respective trunk or branch occlusion (APASS, 1990, 1993b). As for the antiphospholipid syndrome in general, cerebral infarction associated with antiphospholipid antibodies affects a younger population (mean age <50 years) than in typical atherothrombotic stroke (APASS, 1990, 1993b; Levine et al., 2002). Also, there is a female, but no racial, predilection.

The mechanisms of TIA and stroke related to antiphospholipid syndrome are probably heterogeneous. They include embolism from cardiac source, a hypercoagulable state, and endothelial injury (Greaves, 1999; Levine et al., 2002; Gezer, 2003). Left-sided valve thickening, myxomatous degeneration, verrucous endocarditis, or intracardiac clots can be demonstrated by echocardiography in a high percentage of patients with antiphospholipid syndrome and may represent a possible source of thrombi (Vianna et al., 1994; Turiel et al., 2005). Furthermore, antiphospholipid antibodies are associated with a hypercoagulable state, for which several pathophysiological mechanisms have been proposed. One is the interference with function of various phospholipid-binding proteins, such as β_2-glycoprotein I (β_2-GpI), prothrombin, protein C, or annexin V (Oosting et al., 1993). The binding of antiphospholipid antibodies to the natural anticoagulants protein C and β_2-GpI results in their inactivation, thus promoting the coagulation pathway and platelet aggregation (Oosting et al., 1993; Meroni et al., 1998). Antiphospholipid antibodies also interact with endothelial cells, upregulating the expression of adhesion molecules (Meroni et al., 2000). In addition, thrombosis is thought to be promoted by antagonism of prostacyclin production, complement activation, or fibrinolytic dysfunction (Levine et al., 2002; Gezer, 2003). The third putative hypothesis on the etiology of ischemic stroke proposes oxidant-mediated injury of the vascular endothelium. Thereby, antiphospholipid antibodies bind to oxidized low-density lipoproteins. These complexes are taken up by macrophages, which are activated and then cause damage to endothelial cells (Ames, 1994).

45.4.3. Diagnosis and treatment

According to a recent international consensus statement (Wilson et al., 1999), at least one clinical (vascular thrombosis, pregnancy morbidity) and one laboratory criterion (anticardiolipin antibodies, lupus anticoagulant) should be present for a diagnosis of antiphospholipid syndrome (Table 45.18). None of the other features, as listed in Table 45.15, are included because their association with antiphospholipid syndrome is less reliable. Because of the heterogeneity of antibodies in antiphospholipid syndrome, laboratory investigation should include both coagulation-based tests for lupus antibodies and solid-phase immunoassays for anticardiolipin antibodies, since both tests are positive in only about 50% of cases of definite antiphospholipid syndrome (Greaves, 1999; Levine et al., 2002; Gezer, 2003). It is also recommended to assess persistence of antiphospholipid antibodies over time to exclude transient elevation of antibody titers that may not have any clinical significance. A still unresolved issue are the limitations of the laboratory methods with poor consistency between them, which seems to be true especially for commercial reagents and kits (Reber et al., 1995). Thus, systematic testing of antiphospholipid antibodies in ischemic stroke, and especially in the elderly patient, is not warranted (Heinzlef et al., 2001). Even more, since in recent large prospective trials the presence of antiphospholipid antibodies did not influence the risk for subsequent thrombo-occlusive events (APASS, 1997; Levine et al., 1997; APASS, 2004), except for certain subgroups of patients, testing positive for both, lupus antibodies and anticardiolipin antibodies (APASS, 2004). Thus, possible reasons to screen patients for antiphospholipid antibodies include ischemic eye, brain, or spinal cord events in young patients (age <45 years) without any evident cause, any patient with stroke in the context of rheumatic and connective tissue disorders, any patient with recurrent thrombosis or if one or more clinical and laboratory features suggest antiphospholipid syndrome.

In this context, the indication for long-term anticoagulation with warfarin after a first ischemic stroke in association with antiphospholipid syndrome remains controversial. Earlier studies indicating the need for high-intensity anticoagulation were retrospective, had small sample size, and were not double-blinded (Rosove and Brewer, 1992; Khamashta et al., 1995). However, two recent double-blind, randomized clinical trials raise doubts concerning earlier therapeutic recommendations (Crowther et al., 2003; APASS,

Table 45.18

International consensus statement on preliminary criteria for the classification of the antiphospholipid syndrome

Clinical criteria		
	Vascular thrombosis	
		$\geq$1 clinical episode of arterial, venous or small-vessel thrombosis in any tissue group or organ
	Complications of pregnancy	
		$\geq$3 unexplained consecutive spontaneous abortions before the 10th week of gestation; or $\geq$ 1 unexplained death of a morphologically normal fetus at or beyond the 10th week of gestation; or $\geq$ 1 premature birth of a morphologically normal neonate at or before the 34th week of gestation
Laboratory criteria		
	Anticardiolipin antibodies	
		IgG or IgM antibodies present at moderate or high levels on two or more occasions, at least 6 weeks apart
	Lupus anticoagulant	
		Present in plasma on two or more occasions, at least 6 weeks apart
A definite diagnosis of antiphospholipid syndrome requires the presence of at least one clinical and one laboratory criterion		

Adapted from Wilson et al., 1999.

2004). In patients with antiphospholipid antibodies and a history of thrombosis, high-intensity anticoagulation with an international standardized ratio (INR) of 3 to 4 was not superior to moderate adjusted-dose coumarin (INR of 2 to 3) for thrombosis prevention (Crowther et al., 2003). However, the recurrence rate was lower than anticipated, and the study may have been underpowered to show a difference. In a subgroup of unselected stroke patients from the Warfarin Aspirin Recurrent Stroke Study, rates of thrombo-occlusive events over a 2 year follow-up were the same for both treatment groups (325 mg aspirin versus warfarin with a target INR of 1.8–2.8) (APASS, 2004). Furthermore, any treatment strategy should consider the elevated risk of bleeding on high-intensity coumarin treatment, and the difficulties of monitoring the level of anticoagulation in patients with antiphospholipid syndrome due to the lack of standardized reagents and possible interference of antiphospholipid antibodies with this measurement (Moll and Ortel, 1997). Thus, until the issue of optimal secondary prophylaxis in antiphospholipid syndrome is clarified by further controlled prospective studies, more empiric clinical criteria, such as age, concomitant vascular risk factors, and laboratory findings (e.g., levels of antiphospholipid antibodies; presence of both lupus antibodies and anticardiolipin antibodies) should be taken into account for the therapeutic decision. Anticoagulation should be considered in young patients, without additional vascular risk factors and elevated antibody titers of anticardiolipin antibodies or presence of lupus antibodies. All other patients should receive aspirin. Several other therapeutic approaches including corticosteroids, immunosuppressants, plasmapheresis, intravenous gamma globulins, and anti-idiotype antibodies have been tried more on an anecdotal basis and with various outcomes (Gezer, 2003).

45.4.4. Sneddon's syndrome

Sneddon's syndrome is another related condition, which consists of recurrent cerebral ischemia and livedo reticularis (Sneddon, 1965) often accompanied by antiphospholipid antibodies (Frances et al., 1999). In addition it may be accompanied by hypertension, memory disturbances, and retinal vascular obstruction (Rebollo et al., 1983). It is now regarded as a common clinical manifestation of different disease entities. It has been divided into idiopathic, autoimmune, and thrombo-embolic subsets or in systemic lupus erythematosus-associated, antiphospholipid syndrome-associated, and primary forms. Familial occurrence of Sneddon's syndrome is rare. Impairment of coagulation involving factors V, VII, protein S, protein C, antibodies to prothrombin, or, most recently, protein Z deficiency may be occasionally detected in patients with antiphospholipid antibody-negative Sneddon's syndrome (Bolayir et al., 1999; Frances et al., 1999; Besnier et al.,

2003; Ayoub et al., 2004). For accurate diagnosis, various laboratory investigations (e.g., antiphospholipid antibodies, venereal disease research laboratory test, electrophoresis, coagulation proteins, etc.), brain imaging studies (MRI) and skin biopsy are recommended (Stockhammer et al., 1993). The optimum treatment for Sneddon's syndrome is still unclear. Anecdotal reports described a lack of response to immunosuppressive therapy. Some patients respond to either warfarin or aspirin, but, perhaps reflecting the heterogeneity of this syndrome, other patients fail to respond to either drug (Frances et al., 1999).

45.5. Other hematologic diseases associated with stroke

45.5.1. Hyperhomocysteinemia

Hyperhomocysteinemia is a consequence of either disturbed remethylation to methionine or transsulfuration to cysteine (Fig. 45.3). Severe hyperhomocysteinemia (>100 μmol/l) is found in congenital homocystinuria (e.g., deficiency of cystathionine β-synthase or N^5,N^{10}-methylenetetrahydrofolate reductase [MTHFR]) (Mudd et al., 1985; Goyette et al., 1995). Moderate (15–30 μmol/l) or intermediate (30–100 μmol/l) hyperhomocysteinemia is caused by defects in genes encoding for enzymes of homocysteine metabolism (e.g., C667T mutation of the MTHFR gene), by inadequate intake of these vitamins that are involved in homocystinuria metabolism (folic acid, cobalamin, and vitamin B6) or by other medical conditions as renal dysfunction (Diaz-Arrastia, 2000). Epidemiological and clinical studies have proven hyperhomocysteinemia to be an independent risk factor for atherosclerotic diseases and venous thrombosis (Bostom et al., 1999; Wald et al., 2002). Homocysteine plasma levels above the 95th percentile were found to be associated with a two- to threefold elevated relative risk for deep-vein thrombosis and pulmonary embolism. Moreover, mild hyperhomocysteinemia has been shown to be associated with a two- to four-fold increased relative risk for coronary artery disease, cerebrovascular disease, and peripheral arterial occlusive disease (Welch and Loscalzo, 1998; Bostom et al., 1999; Hankey and Eikelboom, 1999; Diaz-Arrastia, 2000; Kelly et al., 2002; Wald et al., 2002). In a recent meta-analysis, the pooled mean homocysteine level in patients with ischemic stroke was found to be 2.32 μmol/l greater compared to that in controls without cerebrovascular events, and a significant association of hyperhomocysteinemia

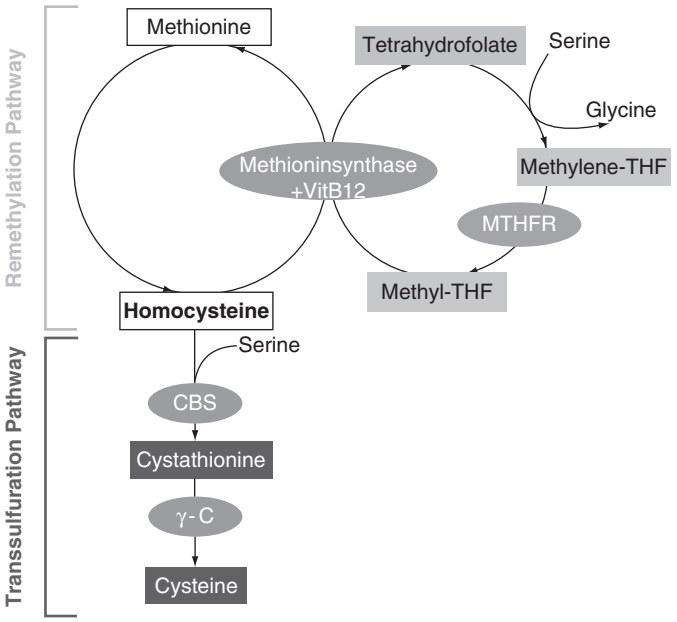


Fig. 45.3. Homocysteine metabolism. In the remethylation pathway, vitamin B12-dependent methionine synthase catalyzes the transfer of a methyl group from methyl-tetrahydrofolate to homocysteine, producing tetrahydrofolate and methionine (methionine cycle). In the folate cycle, free tetrahydrofolate accepts single carbon units from serine to form methylene-tetrahydrofolate and glycine. Methyl-tetrahydrofolate is formed by the reduction of methylene-tetrahydrofolate by methylene tetrahydrofolate reductase. In the trans-sulfuration pathway, cystathionine β-synthase catalyzes the synthesis of cystathionine from homocysteine. The pathway continues with the synthesis of cysteine by cystathionase. Cysteine is a rate-limiting precursor for glutathione synthesis.

and stroke with a pooled odds ratio (OR) of 1.72 (95% CI 1.61–2.0; $p < 0.001$) was also revealed. However, the TT-genotype, a common polymorphism in the MTHFR gene predisposing to hyperhomocysteinemia in vivo, was not significantly more prevalent in stroke patients (Kelly et al., 2002). Thereby, hyperhomocysteinemia seems more prevalent in stroke of microangiopathic origin, diagnosed clinically on the basis of multi-infarction dementia or gait disturbances and the presence of white matter lesions on computed tomography (CT) or magnetic resonance imaging (MRI) (Fassbender et al., 1999). Whereas the exact pathophysiological mechanisms are unknown, several hypothesis have been proposed by which hyperhomocysteinemia contributes to atherogenesis and thrombogenesis (endothelial damage or dysfunction, activation of monocytes or coagulation, dysregulation of lipid biosynthesis, stimulation of smooth muscle cell proliferation) (Welch and Loscalzo, 1998; Lentz, 2005). Diagnosis of hyperhomocysteinemia is complicated by the lack of consensus criteria. Besides the mode of measurement (fasting plasma levels or after methionine challenge), the patient's age and the temporal relationship to the cerebrovascular event play an important role (Hankey and Eikelboom, 1999; Diaz-Arrastia, 2000; Bushnell and Goldstein, 2002a). Several studies have shown that hyperhomocysteinemia can be corrected by supplementation of folic acid, cobalamin, and vitamin B6 (Clarke and Armitage, 2000). However, clinical trials investigating the preventive effect of supplementation of these vitamins on cardiovascular diseases are less conclusive or still under way (VITATOPS—Vitamins to Prevent Stroke Trial Study Group, 2002; Toole et al., 2004; Clarke et al., 2005).

45.5.2. Hematological particularities in gynecology and obstetrics

45.5.2.1. Hormonal therapy

The use of oral contraceptives (OC) is associated with a three- to six-fold increased risk for venous thrombosis in otherwise healthy women (WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception, 1995). Studies have also shown an increased risk of ischemic stroke in women taking the oral contraceptive pill (with an overall odds ratio of about 3.0) (WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception, 1996b). Hemorrhagic stroke was not related to oral contraceptive use, except in developing countries (WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception, 1996a). The risk of stroke further increases in the association of oral contraceptive and other vascular risk factors or hereditary thrombophilias (e.g., factor V Leiden mutation, prothrombin mutation) (Slooter et al., 2005). Hormone replacement therapy in women is also associated with an increased risk of venous thrombosis (two- to four-fold) or ischemic stroke (two-fold) (Daly et al., 1996; Lemaitre et al., 2002). Various effects on hemostasis have been demonstrated by which estrogen and progesterone enhance the formation of thrombi (increased levels of procoagulants, resistance to protein C, altered fibrinolysis) (Koh et al., 1999).

Thrombosis has also been described as a risk with assisted reproductive treatment, particularly in association with ovarian stimulation. In the setting of ovarian hyperstimulation syndrome, venous and arterial thrombo-embolism have been reported (Stewart et al., 1997; Baumann and Diedrich, 2000). Coagulation studies have been limited but generally show increased coagulation factors (fibrinogen, factor VIII) and decreased fibrinolysis. Underlying thrombophilias have not been detected in these women; however, some had a history of prior thrombosis or a positive family history of thrombosis (Stewart et al., 1997). Although the optimal drug and dosing regimen is unknown, a prophylaxis seems prudent in such circumstances.

45.5.2.2. Pregnancy and puerperium

During pregnancy and particularly puerperium women are at risk of thrombo-embolic events due to physiological changes contributing to a hypercoagulable state. This seems to be true for cerebral venous thrombosis, whereas in ischemic and hemorrhagic stroke the causal relationship is less certain (Mas and Lamy, 1998). Women with thrombophilia have an increased risk for venous and arterial thrombo-embolism as well as for gestational vascular complications (e.g., fetal loss, pre-eclampsia, placental abruption, and fetal growth restriction) (Hoffman and Brenner, 2005). Heritable thrombophilia is present in about 15% of Western populations and underlies at least 50% of gestational venous thromboses. Thus, the procoagulant changes during pregnancy can unmask hereditary thrombophilia (Greer, 2003).

Possible hematological mechanisms of amniotic fluid embolism leading to stroke have been discussed in the section on disseminated intravascular coagulation. Pre-eclampsia, characterized by arterial hypertension, edema, and proteinuria may be accompanied by various neurological symptoms (headache, dizziness, blurred vision, altered consciousness), seizures, and stroke. The precise mechanisms are poorly understood, but hematological alterations are of minor importance (Mas and Lamy, 1998). HELLP syndrome (a combination of hemolysis, elevated liver enzymes, and low platelet count) is a severe variant

of pre-eclampsia that frequently leads to devastating neurological consequences such as intracerebral hemorrhage. The mechanisms leading to microangiopathic hemolytic anemia and disseminated intravascular coagulation are still uncertain.

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Chapter 46

Stroke related to systemic illness and complicated surgery

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Previous chapters have been focused on well-known causes of stroke. In the present chapter, the etiological mechanisms that can cause a stroke as a complication of systemic illness (including cancer) and surgery (mainly cardiac and vascular surgery, but also in organ transplantation) are discussed. Although they are uncommon causes of stroke, their knowledge is important to better care for patients, both to prevent stroke and to manage acute stroke in case it should occur. Due to length limitation, we have not described with detail the main systemic clinical features of the illness that can cause a stroke as a complication, and have instead focused only on the etiological mechanisms and specific therapeutic implications in each disease. General principles of investigation procedures, acute stroke management, and stroke prevention are discussed in other chapters of this book. We have structured the present chapter in three main sections: stroke related to systemic illness, stroke related to cancer, and stroke complicating surgery.

46.1. Stroke related to systemic illness

Stroke can appear as a complication of multiple systemic illnesses: inherited disorders; connective tissue diseases and vasculitides; hypercoagulable states and other hematological disorders; metabolic and endocrine disorders; gastrointestinal diseases; renal diseases; liver diseases; and cancer (Table 46.1). Since other chapters of this book are dedicated to some of these etiologies of stroke, we will focus on some of the connective tissue diseases that can cause stroke by mechanisms other than vasculitides, and metabolic or endocrine disorders and cancer.

46.1.1. Connective tissue diseases

46.1.1.1. Systemic lupus erythematosus

Cerebrovascular disease in patients with systemic lupus erythematosus (SLE) is a common complication affecting up to 8–22% of patients (Jennekens and Kater, 2002a) with high rates of recurrence (Futrell and Millikran, 1989). Several etiopathogenic mechanisms are involved: antiphospholipid antibodies, vasculitis and small-vessel vasculopathy, dissection, thrombosis of arteries and veins, abnormalities of coagulation, emboli from several valvular heart diseases, and atherosclerosis (Jennekens and Kater, 2002b). As some of them have been extensively discussed in previous chapters, we focus on the embolic and atherosclerotic mechanisms. Valvular heart disease in patients with SLE can be detected in 53–61% of patients by transesophageal echocardiography. It includes Libman–Sacks or nonbacterial thrombotic endocarditis, valve thickening, valve regurgitation (Roldan et al., 2005), and valve calcification (Molad et al., 2005). Libman-Sacks vegetations can be found in 1 of 10 patients with SLE and they are associated with lupus duration, disease activity, anticardiolipin antibodies and antiphospholipid syndrome manifestations. A long follow up echocardiography study has reported a progression of valve lesions in SLE patients (Moyssakis et al., 2007). Atherosclerosis is another pathogenic mechanism for stroke in SLE patients. Although classic risk factors for atherosclerosis are often present in these patients, they do not fully explain the risk for stroke (Esdaile et al., 2001; Bessant et al., 2004), and SLE itself seems to contribute to the risk of coronary arterial disease and cerebrovascular events. Prolonged glucocorticoid therapy, long duration of SLE, postmenopausal status, and heart failure have been identified

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Table 46.1

Systemic diseases that can cause stroke

Inherited disorders	*Methabolic and endocrine disorders*
Homocystinuria	Diabetes mellitus
Fabry's disease	Hypertension
Marfan's syndrome	Metabolic syndrome
Ehler-Danlos syndrome	Hyperhomocysteinemia
Pseudoxantoma elasticum	*Hypercoagulable states*
Neurofibromatosis type 1	Antiphospholipid antibody syndromes
Sneddon's syndrome	Antithrombin III deficiency
Rendu–Osler–Weber's syndrome	Protein C deficiency
Susac's syndrome	Protein S deficiency
Eales disease	Activated protein C resistance with or without factor V Leiden mutation
Hypereosinophilic syndrome	Prothrombin G20210 mutation
Cerebral amyloid angiopathy	Afibrinogenemia
CADASIL	Hypoplasminogenemia
Vasculitis	Abnormal plasminogen
Predominantly large-vessel vasculitides	Plasminogen activators deficiency
Takayasu's arteritis	Secondary hypercoagulable states: malignances, treatment-related, pregnancy-puerperium and others.
Giant cell arteritis	*Hematological disorders*
Behçet's disease	Policythemia vera
Predominantly medium-vessel vasculitides	Sickle cell disease
Polyarteritis nodosa	Essential thrombocytemia
Primary angiitis of the central nervous system	Thrombotic thrombocytopenic purpura
Predominantly small-vessel vasculitides	Disseminated intravascular coagulation
Wegeners's granulomatosis	Hemophilia
Secondary forms of vasculitis	*Gastrointestinal diseases*
Connective tissue disorders	Inflammatory bowel disease
Paraneoplastic	*Renal diseases*
Infection	Renal failure
Drug-induced vasculitis	Nephrotic syndrome
Connective tissue disorders	*Liver diseases*
Systemic lupus erythematosus	Cirrhosis
Rheumatoid arthritis	*Cancer*
Scleroderma	
Sjögren's syndrome	
Sneddon's syndrome seccondary to antiphospholipid syndrome	

as risk factors for atherosclerosis in epidemiological studies. The current pathogenic hypothesis involves an inflammatory response, the effect of the treatment used, and the presence of the classic risk factors (Meyer, 2001; Jennekens and Kater, 2002b; Frostegård, 2005). On the other hand, recent studies have pointed out the positive correlation between mitral annulus calcification or aortic valve calcification and premature diffuse atherosclerosis, coronary arterial disease, and stroke in young SLE patients (Molad et al., 2006). Thus there is growing evidence that atherosclerosis is an important feature in SLE patients and contributes to the high risk of stroke. A higher prevalence of hypertension, hyperlipidemia and smoking in SLE patients as compared to age-matched controls has been found (Bessant et al., 2006). This fact strengthens the importance of controlling for risk factors for atherosclerosis in these patients. Although few studies have achieved outcome of stroke in patients with SLE, it has been shown that outcome is generally similar between patients with SLE and those without SLE, except for a long length of stay in men with SLE (Ward, 2004). However, it has been recently reported that severe ischemic strokes in SLE patients are not uncommon, affecting to 77% of patients with SLE and first ever stroke in a longitudinal study with a mean follow-up of 8 years from SLE diagnosis. The factors that were related with stroke severity were disease activity, hyperlypidemia and hypertension (Mikdashi et al., 2007).

46.1.1.2. Rheumatoid arthritis

Epidemiological studies have reported an excess of cardiovascular mortality in patients with rheumatoid arthritis, but the possible association with an increased risk for stroke remains controversial due to the lack of

studies analyzing this point. The main pathogenic mechanism involved in this high risk of cardiovascular events seems to be the development of atherosclerosis (Meyer, 2001). Inflammation with increased levels of cytokines and C-reactive protein and the effects of several drugs such as corticosteroids or metotrexate have been pointed out as possible factors contributing to atherosclerosis in patients with rheumatoid arthritis.

46.1.2. Metabolic or endocrine disorders

46.1.2.1. Hypertension

Hypertension is known to be one of the most important risks factors for stroke and has been dealt with in previous chapters, but should be discussed here to highlight that it is a systemic disease causing multiple organ damage. Hypertensive patients with ischemic stroke have different clinical features than non-hypertensive patients: lacunar syndrome, female gender, and previous cerebral infarction have been found as independent variables associated with hypertensive stroke and recurrent stroke is more frequent in these patients (Arboix et al., 2004). Hypertensive encephalopathy, characterized by acute or subacute onset of lethargy, confusion, headache, visual disturbance and seizures, can occur in patients with chronic hypertension (undertreated or not treated) but also in normotensive patients with other diseases that associate severe hypertension such as renal disease, thrombotic thrombocytopenic purpura; drugs as erythropoietin or immunosuppressive agents; and also during pregnancy (eclampsia) or in post-partum HELLP syndrome (a combination of hemolysis, elevated liver enzymes, and low platelet count) (Dinsdale et al., 1998; Vaugham et al., 2000; Negro et al., 2005; Stott et al., 2005). The pathogenesis of hypertensive encephalopathy is not well known but a "breakthrough of autoregulation," endothelial dysfunction, and disruption of the blood–brain barrier with the development of vasogenic cerebral edema have been pointed out as possible mechanisms (Dinsdale et al., 1998; Vaugham et al., 2000). Magnetic resonance imaging shows increased fluid attenuation inversion recovery (FLAIR) and T2 signals predominantly in the posterior parietal and occipital lobes, with normal or decreased diffusion-weighted image signals. Both symptoms and radiological findings usually resolve within a few weeks. The predominant involvement of white-matter substance in the posterior areas of the cerebrum and the reversibility of symptoms and radiological findings are the reasons why this syndrome is also called "Reversible posterior leukoencephalopathy syndrome" (Hinchey et al., 1996). However, this term has been questioned recently since it is not always reversible, cortical involvement has also been demonstrated, and the imaging abnormalities are not always restricted to posterior regions of the cerebral hemispheres (Bianco, 2005; Stott et al., 2005). It is a medical emergency that requires prompt and effective treatment, with appropriate drugs to lower blood pressure, and the withdrawal of immunosuppressive agents in those cases related to immunosuppressive therapies.

46.1.2.2. Diabetes mellitus

Diabetes mellitus is also a well-known risk factor for stroke, not only for its role in the development of diabetic angiopathy that involves cerebral and carotid arteries but also for the high frequency of the association of diabetes with other cerebrovascular risk factors such as hypertension, dislipemia, or cardiac disease. On the other hand, it is also a systemic disease with multiple organ damage and clinical features, etiological patterns, topography, and outcome of stroke in diabetics differ from non-diabetics (Karapanayiotides et al., 2004; Arboix et al., 2005; Ortega-Casarrubios et al., 2007). Ischemic stroke accounts for more than 90% of cerebrovascular events in diabetic patients, with subcortical infarcts (including lacunes) being more common in these patients. MCA territory infarcts are more frequently seen in non-diabetic patients. Intracerebral hemorrhage is less frequent in diabetic patients than in non-diabetic, and when it occurs, deep hemorrhages are more frequent than lobar hemorrhages. With regards to stroke outcome in diabetic patients there exists some controversy.

46.1.2.3. Metabolic syndrome

Metabolic syndrome has been defined by the National cholesterol education program–adult treatment panel (NCEP–ATPIII) as a combination of three or more of the following: fasting blood glucose level $\geq$ 6.1 mmol/L (110 mg/dl), blood pressure $\geq$130/85 mmHg (either value) or antihypertensive treatment, plasma triglycerides $\geq$1.7 mmol/L (150 mg/dl), plasma high density lipoprotein (HDL) $<$1 mmol/L (40 mg/dl) in men and $<$1.3 mmol/L (50 mg/dl) in women, and waist circumference $>$1,020 mm in men and $>$880 mm in women. More recently, a new definition has been proposed by consensus of the International Diabetes Federation: presence of central obesity plus any two of the following factors: increased triglycerides $>$1.7 mM (150 mg/dl); low HDL-C $<$0.9 mM (40 mg/dl) in males or 1.1 mM (50 mg/dl) in females; raised blood pressure $\geq$130/85 mmHg; raised fasting plasma glucose $\geq$5.6 mM (100 mg/dl) or pre-existing diabetes mellitus or pre-existing abnormal glucose value (Alberti, 2005). The prevalence of this syndrome has not been systematically studied, but it has estimated that it affects up to 26% of the population in the USA

(Malik et al., 2004). In the last few years epidemiological evidence that metabolic syndrome is associated to a higher risk of stroke, even in the absence of diabetes, is accumulating (Koren-Morag et al., 2005; Milionis et al., 2005; Galassi et al., 2006). The metabolic syndrome comprises a cluster of abnormalities in multiple metabolic pathways with hyperinsulinemia, insulin-resistance hyperglycemia, atherogenic dyslipidemia, and hypertension. Hypertension and impaired fasting glucose seem to be the most powerful components of this syndrome related to higher risk of stroke (Koren-Morag et al., 2005). It is also interesting the finding that HDL cholesterol loses its protective role against ischemic stroke (Milionis et al., 2005). Treatment should involve lifestyle changes as well as pharmacological treatment of hypertension, hyperglycemia, and dyslipidemia.

46.1.2.4. Hyperhomocystinemia

Homocysteine (Hcy) is an amino acid intermediate formed during the metabolism of methionine, an essential amino acid derived from dietary protein. Total serum levels of homocysteine can be elevated by different causes: hereditary deficiencies in enzymes necessary for the metabolism of Hcy as homocystinuria types I (cystathionine beta synthase deficiency) and II (methylenetetrahydrofolate reductase (MTHFR) deficiency), inborn errors of B12 vitamin metabolism and T667C mutation in the MTHFR; acquired causes such as dietary deficiency of folate, vitamin B6, or vitamin B12; systemic disorders such as chronic renal failure, hepatic failure, hypothiroidism, cancer; some drugs (metotrexate, trimetropin, phenytoin, carbamacepine, topiramate, niacine, teofiline, ciclosporine); smoking; and excessive consumption of coffee (Sepúlveda-Sánchez et al., 2004). Serum total Hcy concentration increases with age and is higher in males than in females. Although mild hyperhomocysteinemia is quite prevalent in the general population (Jaques et al., 1999; Selhub et al., 1999), in the last few years it has emerged as a vascular risk factor (Abbate et al., 2003; Díaz and Sempere, 2004). Animal models have demonstrated that hyperhomocysteinemia is a potent inducer of endothelial dysfunction and can promote atherosclerosis and thrombosis (Lentz, 2005). Retrospective case-control studies and meta-analysis have shown a strong association between levels of Hcy and cerebrovascular disease (Boushey et al., 1995; Møller et al., 2000; Homocysteine Studies Collaboration, 2002; Kelly et al., 2002; Wald et al., 2002). However, data from prospective studies are controversial. While some studies found a positive association between Hcy levels and risk for first-ever stroke (Perry et al., 1995; Bostom et al., 1999; Bots et al., 1999; Tanne et al., 2003; Sacco et al., 2004) and recurrent stroke (Del Ser et al., 2001; Boysen et al., 2003), other prospective studies failed to show a significant association (Alftham et al., 1994; Verhoef et al., 1994; Fallon et al., 2001). A possible explanation for the discrepancies between studies is the time to Hcy determination, since a significant increase in them has been demonstrated in the first days and months from a stroke (Meikejohn et al., 2001; Howard et al., 2002). One interesting point to note is the possible modification of stroke risk by dietary supplementation with B-vitamins and folic acid and several randomized controlled trials have been developed. However, in VISP study the moderate reduction of total Hcy had no effect on vascular outcomes over 2 years of follow-up (Toole et al., 2004). The findings of ongoing clinical studies with vitamin therapy and a meta-analysis of them to achieve adequate statistical power will answer this question (Clarke, 2005).

46.1.3. Gastrointestinal disorders

46.1.3.1. Inflammatory bowel disease

Both Crohn's disease and ulcerative colitis can be complicated with thrombo-embolic stroke and cerebral venous thrombosis (Mayeux and Fahn, 1978; Talbot et al., 1986). Stroke may be more common in patients with ulcerative colitis than in patients with Crohn's disease. Arterial disease is more prevalent than venous and dural sinus disease, and is correlated with an active phase of inflammatory bowel disease (Johns, 1991). The higher prevalence of stroke in inflammatory bowel disease may be related to a hypercoagulable state associated with it, but a possible role of cerebral vasculitis (Nelson et al., 1986; Schluter et al., 2004) and hyperhomocysteinemia (Penix, 1998; Papa et al., 2001; Romagnuolo et al., 2001; Younes-Mhenni et al., 2004; Mahnood et al., 2005) has also been pointed out. Reactive thrombocytosis, increased levels of factors V, VIII, and fibrinogen and antithrombin III deficiency, protein S deficiency (Vaezi et al., 1995), and factor V Leiden mutation (Liebman et al., 1998; Haslam et al., 2000) are the main factors that have been associated with the hypercoagulable state in Crohn's disease and ulcerative colitis. Anticardiolipin antibodies are significantly increased in patients with inflammatory bowel disease, but their role in the pathogenesis of stroke is controversial (Mevorach et al., 1996; Aichbichler et al., 1999).

46.1.4. Renal diseases

46.1.4.1. Renal failure

Patients with chronic renal failure are at risk of both ischemic and hemorrhagic strokes, which represent an important cause of mortality and morbidity in these patients. Atherosclerosis, thrombo-embolic disease or

intradyalitic hypotension are the main mechanisms implicated for the development of ischemic stroke. Atherosclerosis in patients with chronic renal failure has specific features that distinguish it from that of the general population: it is more diffuse and distally located, and risk factors other than the usual (such as hypertension, diabetes mellitus, dyslipidemia, and smoking) are involved: accumulation of guanidino compounds that are implicated in the development of endothelial dysfunction; oxidative and carbonyl stress associated with an inflammatory state; hyperhomocystinemia; disturbances of calcium phosphate metabolism with an increased risk of vascular calcification, arterial stiffness and worsening of atherosclerosis; and detrimental effects of some therapies used in chronic renal failure: dialysis or immunosuppressive agents in renal transplant recipients. Cardiopathies such as dilated myocardiopathy or arrhythmias are other possible complications of renal failure, which in turn can also be a cause of ischemic strokes. Hypotension associated with dialytic treatment is an important issue in these patients since it can be involved in the development of watershed cerebral infarctions. On the other hand, several factors such as hypertension, platelet dysfunction, and the use of anticoagulation or platelet antiaggregants can be implicated in the development of hemorrhagic stroke in patients with chronic renal failure (Brouns and De Deyn, 2004).

46.1.4.2. Nephrotic syndrome

Nephrotic syndrome is characterized by proteinuria due to abnormal increase of glomerular permeability and subsequent hypoalbuminemia, hyperlipidemia and edema. Both arterial and venous cerebral thromboses are rare complications of this syndrome (Marsh et al., 1991; Fuh et al., 1992; Chatuverdi, 1993; Pandian et al., 2000; Lin et al., 2002; Yun et al., 2004; Nandish et al., 2006; Fluss et al., 2006). It has been pointed out that the associated hypercoagulable state could be the cause of these thrombotic complications. Prophylactic anticoagulants could be considered in patients with high risk (severe hypoalbuminemia and on diuretics or steroid treatment) in order to reduce the risk of serious cerebral infarction (Yun et al., 2004).

46.1.5. Liver diseases

Few case reports of cerebral infarctions in patients with cirrhosis have been published (Talenti et al., 1994; Pérez et al., 1999). A hypercoagulable state with deficiency of antithrombin III and protein C; and high titers of anticardiolipin antibodies have been reported in cirrhotic patients with strokes. Interestingly, liver transplantation or post-transplant immunosuppressive agents could reduce the anticardiolipin antibodies titers (Talenti et al., 1994).

Some studies have found a higher risk of plaques in carotid artery as well as carotid intima-media thickening in patients with chronic hepatitis suggesting a possible role of hepatitis B and C viruses in the pathogenesis of carotid arteriosclerosis (Ishizaka et al., 2002a; Ishizaka et al., 2002b). However, other epidemiological studies could not find any association between serological markers of hepatitis B or C infection and the risk of atherosclerosis (Völzke et al., 2004). Lately, it has been pointed out that, although seropositivity to hepatitis B virus is associated to an increased risk of hemorrhagic stroke and decreased risk of ischemic stroke and myocardial infarction, these associations appears to be secondary to the liver dysfunction without any influence on the development of atherothrombosis (Sung et al., 2007).

46.2. Stroke related to cancers

Stroke can be a manifestation of cancer, either as a complication in patients with a known cancer or as a first manifestation of it (Bescansa et al., 1985). Few prospective studies to determine the frequency of stroke related to cancer have been performed and the role of the different possible pathogenic mechanisms is in some points speculative since no prospective series with complete diagnostic investigations in stroke patients with cancer have been conducted. Autopsy studies have found pathologic evidence of cerebrovascular diseases in 14.6% of patients with cancer, with 7.4% being symptomatic. Hemorrhagic strokes were more frequently seen in leukemia, whereas ischemic strokes were more common in solid tumors and in lymphomas (Graus et al., 1985). A retrospective study in patients with cancer showed a frequency of documented stroke in 0.12% of all admissions to a cancer center (Cestari et al., 2004). In a neurological setting, two studies have reported that about 4% of stroke consultations and admissions in a university center were patients with cancer, but the most frequent cause of stroke in them was large-vessel atherosclerosis (Chaturvedi et al., 1994; Zhang et al., 2006).

Pathophysiological mechanisms implicated in stroke in cancer patients are varied (Table 46.2). The two most frequent are hematological disturbances and embolism. Direct effects of the tumor include infiltration or mass-effect on artery or venous systems, and intratumoral hemorrhage.

Hematological disturbances are common in cancer patients. Mild shortening or prolonging of the prothrombin time or partial thromboplastine time, elevated levels of fibrinogen and activated coagulation factors, mild to moderate thrombocytosis, and enhanced platelet

Table 46.2

Main proposed etiopathogenic mechanisms for stroke in cancer patients

Direct effect
Haematological disturbances
Thrombocytopenia
Paraneoplastic thrombocytosis
Disseminated intravascular coagulation
Trousseau syndrome
Embolism
Nonbacterial thrombotic endocarditis
Tumor embolism
Paradoxical embolism associated to patent foramen ovale
Septic embolism
Atherosclerosis
Dural sinus thrombosis
Treatment complications
Chemotherapy
Radiation therapy
Hematopoietic stem-cell transplantation

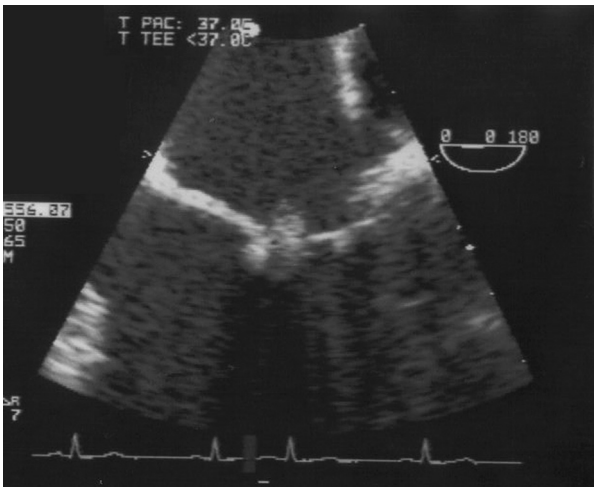

Fig. 46.1. Non-bacterial thrombotic endocarditis in a 51-year-old female patient, presenting with a right middle cerebral artery infarction as initial manifestation of an ovarian cancer.

activity have been reported in these patients, as well as a suppression of fibrinolytic activity. However, laboratory markers are not predictive of thrombo-embolic disease in patients with cancer (Lee, 2002). On the other hand, these hematological disturbances can be produced by the tumor itself but can also be associated with CNS metastasis or with cancer therapies (Bick, 2003; Rogers, 2003, 2004). As a cause of neurological complication, disseminated intravascular coagulation has been the most frequently reported in these patients (Bick, 1992). The underlying mechanism is not well known, but excessive thrombin production leading to increased consumption of platelets, coagulation factors, and inhibitors of coagulation have been proposed as possible causes (Rogers, 2004). It is more frequent in leukemia and lymphoma leading to systemic and brain hemorrhages. Trousseau's syndrome, characterized by the triad of thrombophlebitis, hemorrhage, and arterial emboli, has also been described as a possible cause of stroke (Sack et al., 1977; Tasi et al., 2004; Kwon et al., 2007), although its frequency is unknown.

46.2.1. Embolism

Non-bacterial thrombotic endocarditis (NBTE) (Fig. 46.1) has been reported as a cause of stroke in cancer patients. In an autopsy study NBTE was the most frequent etiology of symptomatic cerebrovascular diseases in cancer patients (Graus et al., 1985), but this could be underestimated in the clinical setting because most studies did not include a transesophageal echocardiography as a part of the stroke evaluation (Cestari et al., 2004; Zhang et al., 2006). In a prospective echocardiographic study of 200 cancer patients, NBTE was identified in 19% of them (Edoute et al., 1997). It has been described in patients with adenocarcinoma, especially in mucin-producing carcinomas of the lung and gastrointestinal tract, and lymphoma (Reisner et al., 2000), but also in gynecological neoplasms (ovarian, cervix). Other possible embolic sources in cancer patients are: tumor embolization to the brain, which has been described more frequently in left atrial myxomas (Fig. 46.2) (Bienfait and Moll, 2001; Frank et al., 2001; Le et al., 2003) but has also been described in nonmyxomatous tumors (cardiac sarcomas, lung tumors) (O'Neill et al., 1987; Imaizumi et al., 1995); paradoxical embolism in patients with patent foramen oval and hypercoagulability state (Mitsui et al., 2001; Ionita et al., 2002; Iguchi et al., 2007); and septic emboli, usually in cancer patients with fungal sepsis (aspergillus, candida) (Fig. 46.3). Cerebral aneurysms and subsequent subarachnoid hemorrhage can occur as result of both tumor and septic emboli (mycotic aneurysms) (Fig. 46.4).

46.2.2. Atherosclerosis

The role of atherosclerosis as a pathogenic mechanism of stroke in cancer patients is controversial. It has been reported that 3.5% of all stroke consultations and admissions in a university center were patients with cancer, but the most frequent cause of stroke in them was large-vessel atherosclerosis (Chaturvedi et al., 1994). But other authors have found atherosclerosis related to the presence of vascular risk factors in only 21-22% of patients

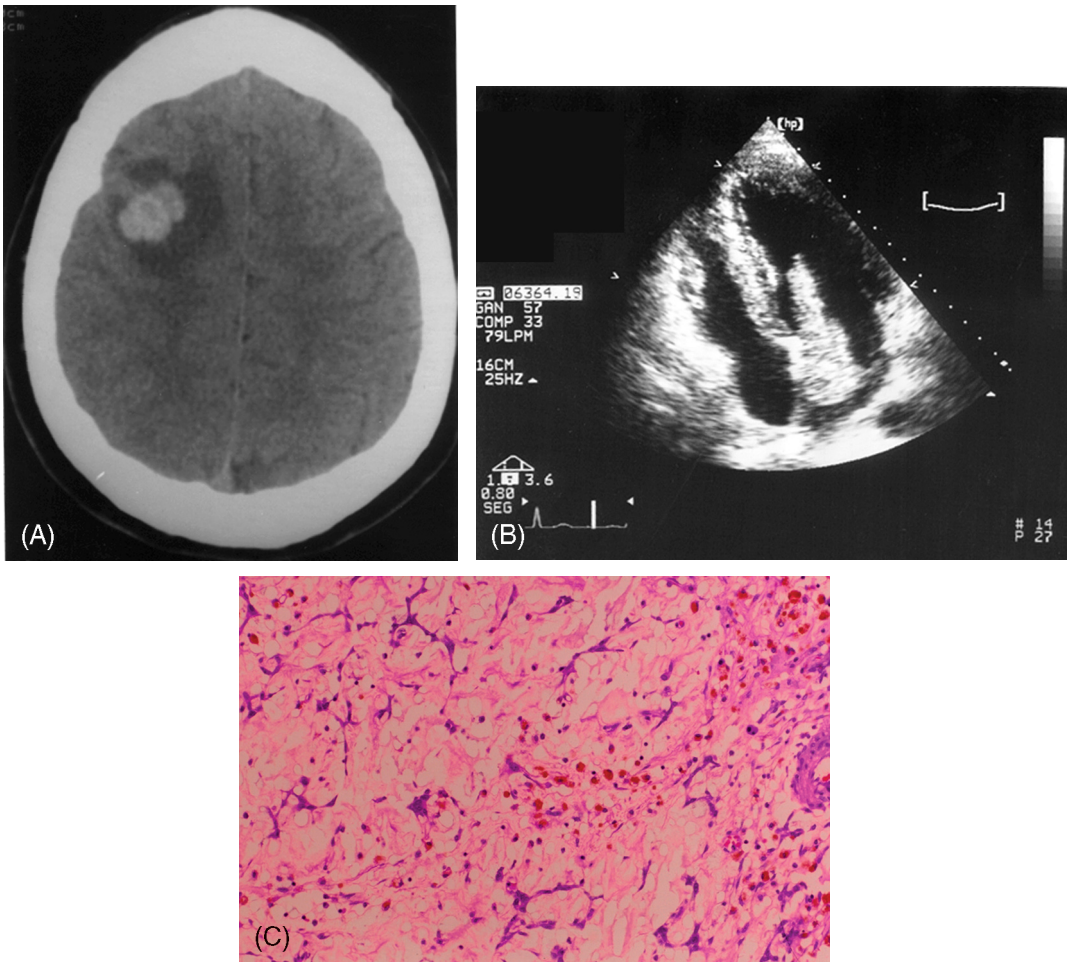

Fig. 46.2. Cerebral hemorrhage as embolic complication of left atrial myxoma. (A) brain TC; (B) echocardiography: left atrial myxoma; (C) histology.

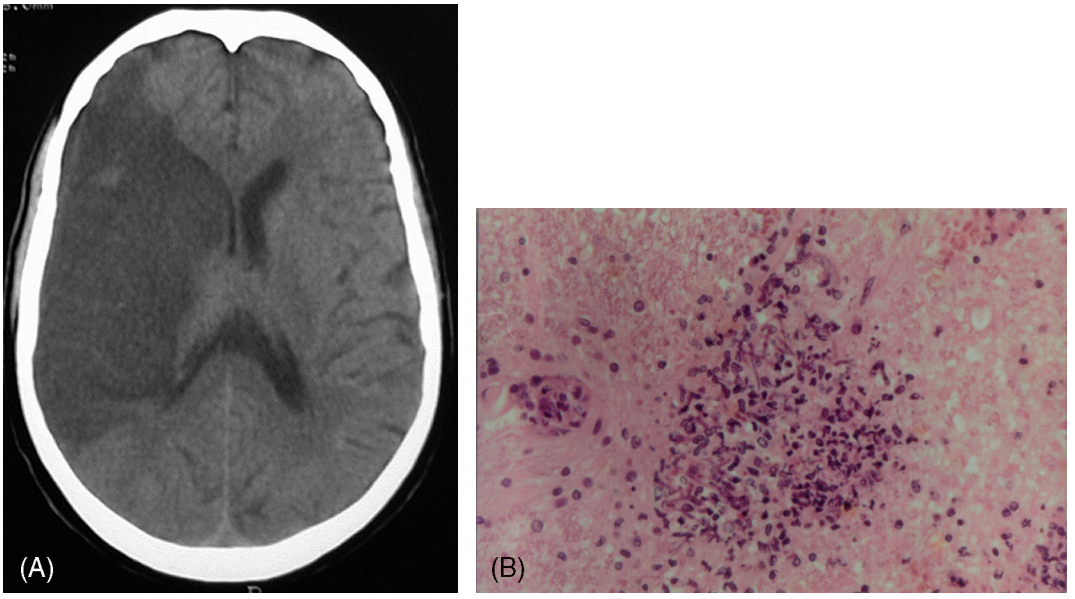

Fig. 46.3. Cerebral infarction secondary to septic embolism (*Aspergillus* sp.) in a patient with multiple systemic and cerebral embolism as a complication of aspergillus aortitis. (A) Brain TC showing right MCA infarction; (B) autopsy findings: cerebral microabscess due to *aspergillus* embolus with arteritis associated.

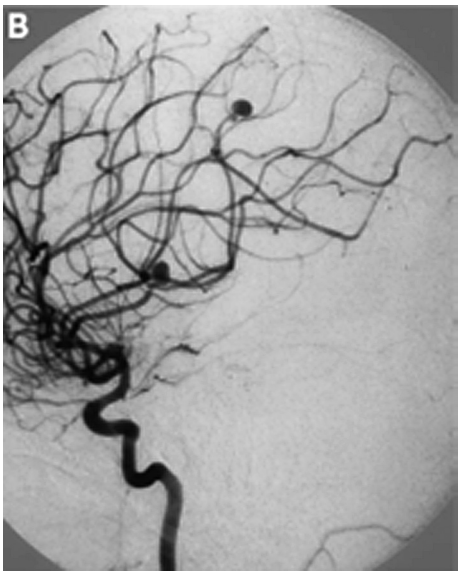

Fig. 46.4. Mycotic aneurysm.

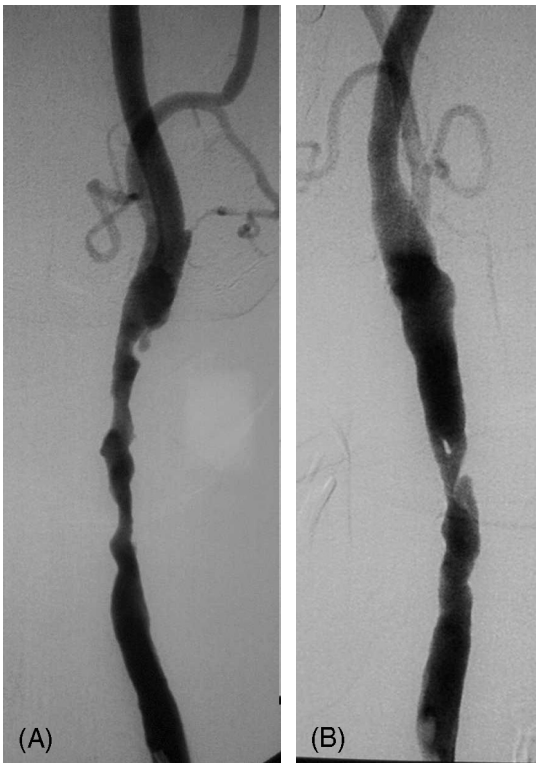

Fig. 46.5. Bilateral primitive carotid stenosis 20 years after radiotherapy. (A) Left-side; (B) right-side.

(Cestari et al., 2004; Zhang et al., 2006). On the other hand, cervical radiotherapy can induce the development of accelerated carotid atherosclerosis (Dorresteijn et al., 2002).

46.2.3. Dural sinus thrombosis

Neoplastic venous sinus occlusion secondary to compression or infiltration has been reported in a wide variety of tumors, but is most frequent in patients with neuroblastoma, lung cancer, and lymphoma (Rogers, 2004). It can also occur with coagulation disorders associated with the tumor, mainly in leukemia and lymphoma, or as an adverse effect of tumor therapy as has been described with L-asparaginase (Gugliotta et al., 1992; Kieslich M, et al., 2003) or tamoxifen (Masjuan et al., 2004).

46.2.4. Treatment complications

Various chemotherapy and hormonal agents used in cancer therapy have been demonstrated to produce systemic and cerebral thrombosis: L-asparaginase (Gugliotta et al., 1992; Kieslich et al., 2003); tamoxifen (Pritchard et al., 1996; Masjuan et al., 2004); 5-fluorouracil; and cisplatin therapy (El Amrani et al., 1998). Therapeutic radiation can induce the development of carotid stenosis or occlusion by accelerating atherosclerosis (Dorresteijn et al., 2002) (Fig. 46.5).

Neuroimaging studies, measurement of coagulation function, and echocardiography are the most useful diagnostic tools to identify the cause of stroke. Treatment will depend on the pathogenic mechanism: therapy of acute disseminated intravascular coagulation comprises the treatment of underlying cancer and the replacement of clotting factors with fresh frozen plasma, cryoprecipitate, and platelets. Heparin may be indicated to stop the thrombotic process and steroids to reduce cerebral edema. NBTE and cerebral intravascular coagulation therapy is also based on the treatment of the underlying cancer and the activated coagulation, heparin being more effective than warfarin in the treatment of this. The usual therapy for radiation-induced atherosclerosis is carotid angioplasty and stenting although no comparative studies of medical versus surgical endovascular treatment have been performed. Treatment of tumor-related venous occlusion consists of brain radiation or chemotherapy, depending on tumor type, and in large tumors that compress dural sinus, surgical resection is indicated (Rogers, 2004).

Few studies have assessed outcome of cancer patients with stroke. Zhang et al (2006) found a higher in-hospital post-stroke mortality than non-cancer stroke controls and Cestari et al (2004) reported a median overall survival of 4.5 months in a retrospective review. Rankin score, stroke etiology, primary

cancer diagnosis, and the presence of metastatic disease affected survival.

46.3. Stroke complicating surgery

Stroke can appear as a complication of surgery, generally as a consequence of embolism or due to cerebral hypoperfusion during procedures. It is very rare in general surgery but has become a feared (although uncommon) complication of cardiac surgery, vascular surgery (carotid endarterectomy and percutaneous transluminal angioplasty of carotid or cerebral arteries), and organ transplantation in the last few years due to the increase in the number of patients under these surgical procedures. The development of a peri-operative stroke worsens patient prognosis and is an important cause not only of mortality but also of morbidity. A better knowledge of the mechanisms conducive to stroke after surgery could help to make technical modifications in order to avoid this complication.

46.3.1. Cardiac surgery

In the last few years the number of patients undergoing cardiac surgery, mainly coronary vascularization procedures, has significantly increased. Technological advances in surgical procedures have achieved a reduction in associated mortality and morbidity, but have also meant an increase in the average age of patients undergoing cardiac surgery. Patients previously deemed inoperable due to the severity of cardiac diseases or to the presence of concomitant diseases with high risk for surgery are now considered suitable candidates. These changes in management of elderly and high-risk patients could explain in part how neurological complications after cardiac surgery remain an important issue.

The spectrum of neurological complications after cardiac surgery is broad, ranging from stroke to subtle cognitive disturbances or to anoxic–ischemic encephalopathy (McKann GM et al., 2006). Neurological complications after cardiac surgery are associated with a higher in-hospital mortality, increased duration of intensive care and post-operative hospital stay, increased patient charges, and increased likelihood of being discharged to an intermediate or long-term care facility (Arrowsmith et al., 2000; Stamou et al., 2001).

Post-operative stroke is the most studied neurological complication after a cardiac surgery. From initial reports in the late 1980s and early 1990s of estimated frequencies of 5% in coronary artery bypass graft (CABG) surgery and 16% in valve replacement surgery, the latest studies pointed out rates of 1.3% in CABG and 1.2% in valve replacement surgery, but with a significant increase in stroke risk when performing both surgical procedures affecting 3.4% of patients (Hogue et al., 1999; Wolman et al., 1999; McKann et al., 2006).

The main pathogenic mechanisms implicated in the development of stroke after cardiac surgery are thrombo-embolism and hypoperfusion associated with the procedure (Likosky et al., 2003; Selim M, 2007) (Fig. 46.6). In the last few years, much effort to identify predictive factors for stroke after cardiac surgery has been made. A retrospective analysis in 16,528 patients who underwent CABG showed that chronic renal insufficiency, recent myocardial infarction, previous cerebrovascular event, carotid artery disease, hypertension, diabetes, age of more than 75 years, moderate/severe left ventricular dysfunction, low cardiac output syndrome, and atrial fibrillation were significant correlates of stroke (Stamou et al., 2001). On the other hand, a multivariate analysis in a prospective series of 16,184 consecutive patients undergoing cardiac surgery that included CABG and valve replacement procedures, revealed ten variables that were independent predictors of stroke: prior cerebrovascular disease, peripheral vascular disease, diabetes, hypertension, previous cardiac surgery, preoperative infection, urgent operation, cardiopulmonary bypass time more than 2 hours, the need for intraoperative hemofiltration, and high transfusion requirement (Bucerius et al., 2003). Prior stroke and the presence of carotid atherosclerotic disease appear to be the factors more importantly associated with stroke after cardiac surgery. Several studies have reported a high risk of post-operative stroke in patients with a history of stroke or TIA (Hogue et al., 1999, 2003). This could be related to the presence of significant atheromatous disease but also to persistent hemodynamic vulnerability in patients with recent stroke (in the 3 months before surgery) (Arrowsmith et al., 2000). The development of atrial fibrillation, that occurs in 30-50% of patients after cardiac surgery, is also a major cause of perioperative strokes (Limburg et al., 1998; Bucerius et al., 2003; McKann et al., 2006; Selim M, 2007). On the other hand, intracranial artery disease has been suggested as an independent factor for neurological complications after CABG surgery in Asian patients (Yoon et al., 2001). The presence of atheromas in the ascending aorta has been pointed out as an important predictive factor for post-operative stroke (Davila-Roman et al., 1999; Mackensen et al., 2003) and their detection could influence the surgical technique based on ultrasonic evaluation of the aorta, such as changes in the position of the aortic cannula, cross-clamp, off-pump CABG, and replacement of ascending aorta. (Hangler et al., 2003; Prasongsukarn et al., 2005; Mckann et al., 2006).

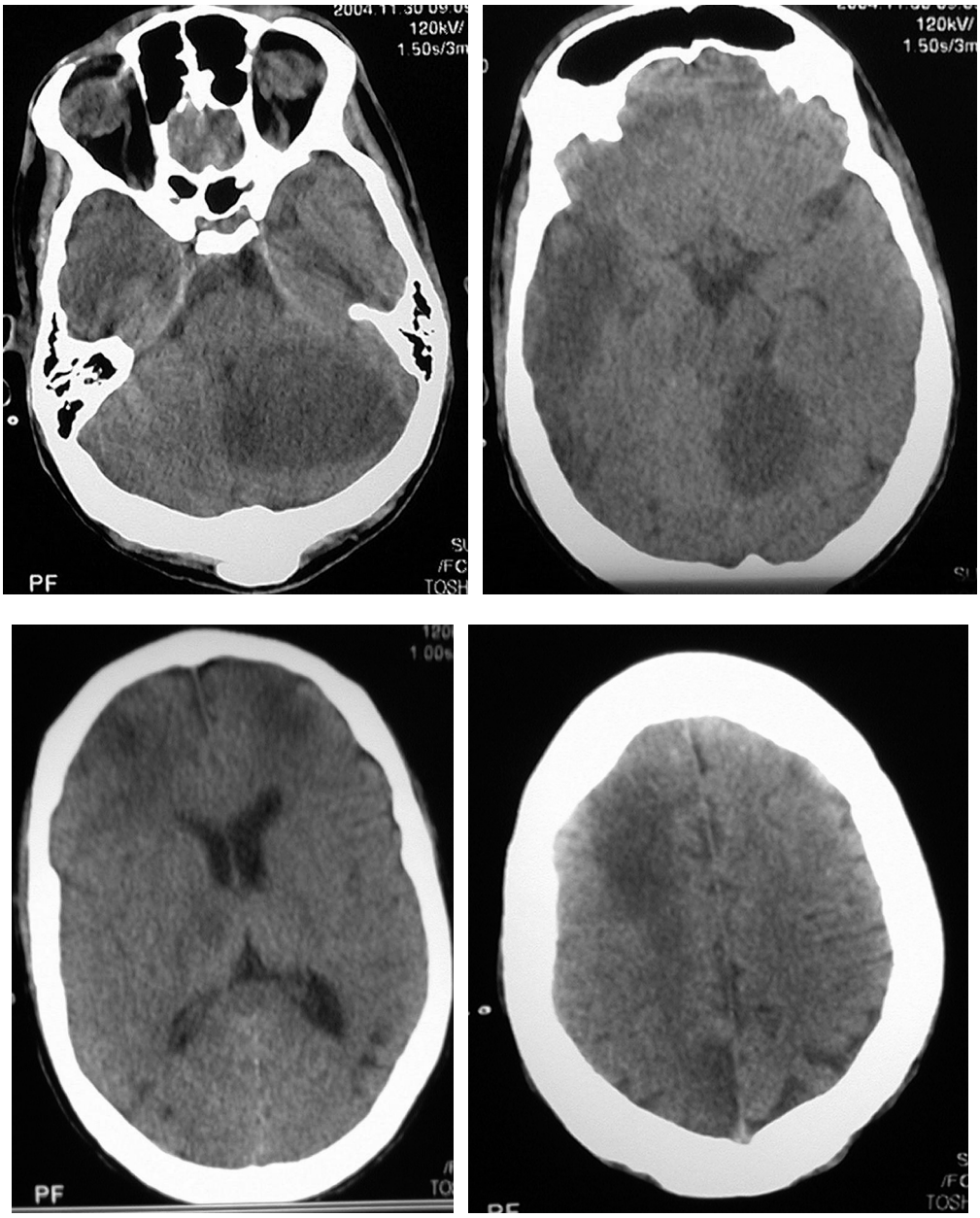

Fig. 46.6. Multiple cerebral infarction as early post-operative complication in a 27-year-old male, who underwent cardiac surgery for tetralogy of Fallot.

46.3.2. Carotid occlusive disease surgery and endovascular procedures: carotid endarterectomy, carotid artery angioplasty and stent placement

46.3.2.1. Ischemic stroke after carotid surgery or endovascular procedures

Two mechanisms have been implicated in the development of ischemic stroke complication of carotid surgery: cerebral embolization during dissection of the carotid artery and from the endarterectomy surface, and hypoperfusion during clamping of the carotid artery (Fig. 46.7). Endovascular therapy of carotid occlusive disease has been introduced as an alternative to carotid endarterectomy. Although peri-procedural stroke due to hypoperfusion related to luminal compromise by catheters and guidewires crossing the stenotic lesion or during balloon inflation is possible, it is less frequent than in carotid endarterectomy. However, the rates of embolization detected by transcranial Doppler are significantly higher in endovascular procedures.

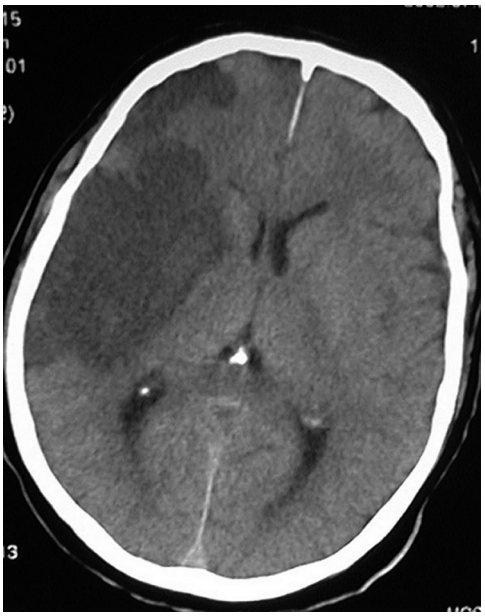

Fig. 46.7. Peri-operative right MCA cerebral infarction in a 64-year-old male who underwent a right carotid endarterectomy.

46.3.2.2. Carotid endarterectomy

A North American Symptomatic Carotid Endarterectomy Trial (NASCET) study reported a peri-operative stroke and death rate of 6.5% with 1.8% of disabling stroke and 3.7% non-disabling stroke in patients with symptomatic severe and moderate carotid stenosis. The majority of peri-operative strokes were ipsilateral to the surgical procedure and occurred early after carotid endarterectomy, within the first 24 hours, and particularly within 6 hours. Variables associated with a significant increased risk for peri-operative stroke and death were: a hemispheric TIA compared to a retinal TIA, a left-sided procedure, the presence of contralateral carotid occlusion, an ipsilateral ischemic lesion on the CT and irregular or ulcerated plaque detected by angiography on the side of surgery (Ferguson et al., 1999) (Table 46.3). The European carotid surgery trial (ECST) study reported similar results: 7.1% death rate and/or stroke at 30 days, and 0.6% fatal stroke. Factors associated with higher risk were cerebral TIA versus ocular ischemic events, female sex, systolic hypertension, and peripheral vascular disease (Bond et al., 2002).

The third randomized study on carotid endarterectomy in symptomatic carotid stenosis, the Veteran Affairs Cooperative Carotid Trial, was prematurely discontinued due to the publication of positive results of the NASCET and ECST studies, and reported a peri-operative surgical stroke and death rate of 5.5% in male patients with carotid stenosis $>50\%$ (Mayberg et al., 1991).

However, when analyzing peri-operative stroke rates we should consider that data from randomized trials have a selection bias, not only in relation to the baseline characteristics of patients but also with regard to participating surgeons, as no surgeon was accepted in the studies whose experience disclosed a peri-operative complication rate of stroke and death higher than 6% as in NASCET. It is true that the comparison from these trials to large case series and community studies is difficult due to different criteria for patient selection and to the lack of a standardized evaluation of peri-operative stroke events, but these latest studies could reflect the real frequency in daily practice. A systematic review of carotid endarterectomy studies from 1980 to 1994 showed a 5.64% risk of stroke and/or death for symptomatic stenosis and 0.86% overall risk of fatal stroke. An interesting finding was that the risk of stroke and/or death was highest in the reports with assessment by a neurologist or physician and lowest in reports with single surgeon authors, suggesting a possible difference of awareness for stroke symptoms (diagnosis bias) between surgeons and neurologists (Rothwell et al., 1996a). A population-based review to identify risk factors for the development of perioperative stroke and/or death after CEA founded an overall rate for stroke and/or death of 6% and risks factors associated were prior TIA or stroke, contralateral carotid stenosis, congestive heart failure, atrial fibrillation and diabetes (Tu et al., 2003). It has also been pointed out that risks of stroke and/or death due to carotid endarterectomy are significantly lower for asymptomatic (3.35%) than symptomatic stenosis (5.18%) (Rothwell et al., 1996b). (Fig. 46.7).

In asymptomatic patients the 30-day peri-operative rate of permanent stroke or death was 1.5% in the asymptomatic carotid atherosclerosis study (ACAS), and 3.1% in the ACST (MRC Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group, 2004). A secondary analysis of peri-operative surgical mortality and morbidity showed that diabetes, contralateral siphon stenosis, alcohol and the length of external carotid artery plaque were associated with a higher risk of peri-operative stroke (Young et al., 1996).

46.3.2.3. Carotid angioplasty

Carotid angioplasty with or without stent placement is the endovascular treatment of choice. Although a systematic review of initial single-center reports on carotid angioplasty showed a two-fold greater risk of stroke after angioplasty than after endarterectomy (Golledge et al., 2000), in the last few years endovascular techniques have been improved in order to limit this complication, with the development of specifically designed carotid stents and cerebral protection devices

Table 46.3

Perioperative stroke after carotid endarterectomy or carotid endovascular procedures. Summary of the main published studies

	No. of patients	Stroke and/or death at 30 days	Non-fatal stroke	Fatal Stroke	Factors associated to higher risk
CEA for symptomatic carotid stenosis					
Randomized studies					
NASCET	2,885 included 1,415 in surgical arm	6.5%	—	0.6%	Hemispheric TIA compared to a retinal TIA, left-side procedure, contralateral carotid artery occlusion, ipsilateral ischemic lesion on the CT irregular or ulcerated plaque detected by angiography on the side of surgery
ECST	3,024 included 1,729 in surgical arm	7.1%	6.1%	0.6%	TIA versus ocular ischemic events Female sex Systolic hypertension Peripheral vascular disease
VA-CSP-309	189	5.5%	—	—	
Non-randomized studies/systematic reviews/ population-based studies					
Rothwell et al. (1996a)	15,956	5.64%	—	0.86%	
Tu et al. (2003)	6,038	6.0%	4.5%	—	Prior TIA or stroke Contralateral carotid artery occlusion Congestive heart failure Atrial fibrillation Diabetes
CEA for asymptomatic carotid stenosis					
ACAS	1,662 721 underwent CEA	1.5%	—	—	Diabetes Contralateral siphon stenosis Never drinking Length of external carotid artery plaque
ACST	3,120 1,348 underwent CEA	3.1%	—	—	
Endovascular procedures					
Randomized studies					
CAVATAS	505 251 in endovascular arm	6.4%	—	—	
SAPPHIRE	159 (endovascular treatment)	4.4% *	—	—	
EVA-3S	261 (endovascular treatment)	9.6	—	—	
SPACE	567 (endovascular treatment)	6.84%	—	—	
CREST (ongoing)	749 (interim analysis)	4.41%	—	—	Age $\geq$ 80
Non-randomised studies/multicenter registries					
CAPTURE	3500 patients	5.7%	—	—	

*stroke, myocardial infarction or death within 30 days.

to collect the embolic debris. Thus, with data from early randomized trials and from a systematic review of the Cochrane Library, carotid angioplasty has been considered to be a secure alternative to carotid endarterectomy in patients with carotid stenosis with similar rates of peri-operative stroke (Coward et al., 2005). The carotid and vertebral artery transluminal angioplasty study (CAVATAS) showed 6.4% rates for

disabling stroke or death in the group of endovascular treatment compared to 5.9% in the surgical arm (CAVATAS investigators, 2001). In the stenting and angioplasty with protection in patients at high rik for endarterectomy (SAPPHIRE) study the cumulative incidence of death, stroke, or myocardial infarction within 30 days after the procedure was 4.8% among patients with carotid stenosis and coexisting conditions that potentially increased the risk by carotid endarterectomy assigned to stent procedures (Yadav et al., 2004). Carotid revascularization endarterectomy versus stent trial (CREST) is an ongoing randomized trial in symptomatic patients with carotid occlusive disease, which will assess the differential efficacy of carotid endarterectomy and carotid artery stenting. In an interim analysis it has reported a 4.41% rate for death or stroke within 30 days, and that this risk is higher (reaching 12.12%) in octogenarian patients (Hobson et al., 2004). Factors that have been identified as independently associated with carotid angioplasty and stenting periprocedural neurological deficits are: advanced age and long or multiple stenoses (Mathur et al., 1998); symptomatic lesion, length of stenotic segment $\geq$11.2 mm and absence of hypercholesterolemia (Qureshi et al., 2000); as well as the type of presenting event (Kastrup et al., 2005). More recently, new randomised trials on carotid stenting versus endarterectomy have found higher rates of stroke and death at day 30 affecting to 6.84% of patients in the SPACE Trial (The Space Collaborative Group, 2006) and to 9.6% in the EVA-3S (Mas et al., 2006). The main criticism that these trials have received are the effect of learning curve in the stenting arm and the no use of protection devices in all the patients. In this sense, there exist some controversies about the use of these protection devices Kastrup et al., 2003; Cremonesi et al., 2003; (EVA-3S investigators, 2004; Forsting et al., 2004; Naylon et al., 2004; Brown et al., 2004, Veselka J et al., 2007; Maynar et al., 2007). On the other hand, in a large multicenter register (CAPTURE) conducted to assess outcomes of carotid angioplasty with stent, in the postapproval setting, the rate of death or stroke at day 30 was 5.7% and major stroke and death was 2.9% (Fairman et al., 2007).

46.3.2.4. Hyperperfusion/reperfusion syndrome

Another feared complication from carotid surgical or endovascular procedures is the development of ipsilateral hemorrhage related to hyperperfusion/reperfusion (Karapanayiotides et al., 2005). This is a rare delayed post-operative complication characterized by transient focal deficits associated with ipsilateral migraine-like headache, seizures, reversible ipsilateral brain edema, and intracerebral hemorrhage. It has been described both in carotid endarterectomy and endovascular carotid procedures but also after a variety of procedures that improve flow to a chronically ischemic hemisphere: subclavian–carotid bypass (Ammar, 1987), subclavian artery endovascular therapy (Salerno and Vitek, 2005), and extracranial–intracranial bypass (Ogasawara et al., 2005). The most widely accepted pathogenic hypothesis for hyperperfusion/reperfusion syndrome is an impaired autoregulation of cerebral blood flow. The incidence of associated intracranial hemorrhage is 0.3–1.2% following carotid endarterectomy, and 0.67% after carotid angioplasty and stenting (Abou-Chebl et al., 2004). Risk factors for the development of this syndrome are: the presence of a critical carotid stenosis $\geq$90%, severe contralateral disease, poor collateral flow, hypertension, and recent stroke or ischemia (Ouriel et al., 1999), although not all studies agree on these factors (Ascher et al., 2003). Nevertheless, the development of cerebral hemorrhage due to a hyperperfusion/reperfusion syndrome impairs significantly the patient prognosis. Identification of patients at high risk and control of blood pressure are the current basis of prevention. A recently published case-cohort study has pointed out the possible benefit of pretreatment with edaravone, a free-radical scavenger (Ogasawara et al., 2004), but no randomized studies with neuroprotectant drugs have been conducted.

46.3.3. Aortic or peripheral vascular surgery

The development of a post-operative TIA or a stroke after non-carotid vascular surgery is an uncommon but feared complication. It affects less than 1% of patients undergoing abdominal aorta surgery, lower extremity revascularization, or major amputation procedures but is associated with a six-fold increase in the risk of death and a significantly longer length of stay (LOS). The pathogenic mechanisms implicated in the occurrence of stroke after aortic or peripheral vascular surgery have not been studied enough, mainly because the majority of studies analyzing this complication are retrospective and based on hospital registries. In any case, the type of stroke (ischemic or hemorrhagic) is not specified and neither are the results of neurological investigations. Age, prior stroke, internal carotid artery stenosis $\geq$50%, peri-operative hypotension, post-operative myocardial infarction, and abdominal aorta surgery are the factors independently associated with a higher risk for stroke (Harris et al., 1992; Axelrod et al., 2004). Type-I aortic dissection can also be complicated with focal or global cerebral ischemia, even within surgical treatment (Blanco et al., 1999).

46.3.4. General surgery

Stroke as a complication of general surgery is very rare, affecting less than 1% of cases, mainly the elderly (Uldry et al., 1992; Kam et al., 1997). The most common mechanism is embolism, and the risk factors associated are previous stroke or TIA, hypertension, cardiac abnormalities, major atherosclerosis, and diabetes mellitus (Uldry et al., 1992). Other possible mechanisms are intra or post-operative hypotension, positional trauma with dissection of neck arteries during general anesthesia, paradoxical embolism from post-operative deep venous thrombosis through a patent foramen ovale, peri-operative myocardial infarction, or atrial fibrillation (Warlow et al., 1996).

46.3.5. Organ transplantation

46.3.5.1. Renal transplantation

Stroke is the most frequent neurological complication in renal transplantation recipients with an estimated prevalence of 8%. The main predictors of stroke are diabetic neuropathy, peripheral vascular disease, and an age of over 40 years. Ischemic stroke is related to the high prevalence of cerebrovascular risk factors in patients with chronic renal failure who underwent a renal transplantation: diabetes, hypertension, dyslipidemia, as has been discussed previously. Cerebral hemorrhage is also a frequent complication in these patients and platelet dysfunction caused by uremia has been pointed out as a possible cause. The outcome is poor, as about 50% of the patients die in the 3 months following stroke (Adams et al., 1986; Oliveras et al., 2003; Ponticelli C and Campise MR, 2005).

46.3.5.2. Liver transplantation

Intracranial hemorrhage has been found in about 24% of autopsied liver transplant recipients (Estol et al., 1991) and 1.5% in clinical series (Bronster et al., 2000) but it is clearly associated with a high mortality (up to 57%). Cerebral infarction appears in less than 2% of liver transplant recipients in clinical series, although data from autopsied series pointed out a higher frequency (3.6–18%). Possible causes are fungal infection, endocarditis, disseminated intravascular coagulation, or antiphospholipid syndrome, and an extensive diagnostic investigation should be carried out looking for these possibilities (Bronster et al., 2000).

46.3.5.3. Cardiac transplantation

Few studies have focused on cerebrovascular diseases as a complication of cardiac transplantation, which occurs in approximately 5–17% of cases. Ischemic stroke is more frequent than hemorrhagic stroke. Multiple peri-operative factors can cause focal or global cerebral ischemia early after a cardiac transplantation including: asystole, embolism, cardiac traumatism, gaseous, fat or foreign-body embolism, coagulation disorders, infections, and complications of cardiac catheterization. Prior stroke increases the risk for perioperative stroke after cardiac transplantation. Hemorrhagic stroke is rare after cardiac transplantation. It has been related to coagulation disorders, high pressure of cardiopulmonary bypass, aspergillosis, uncontrolled blood pressure and a "hyperperfusion mechanism" (Adair et al., 1992; Jarquin-Valdivia et al., 1999; Belvís et al., 2005).

46.3.6. Management of perioperative stroke

Intravenous thrombolysis is contraindicated in those patients who have recently undergone major surgery, and it has been suggested that intraarterial administration of tPA could be a viable therapeutic option in these patients with similar mortality rates to that reported in intraarterial thrombolysis trials (Chalela et al., 2001; Moazami et al., 2001).There are few data on the use of endovascular mechanical clot disruption (Selim M, 2007).

46.3.7. Strategies to avoid perioperative stroke

The modification of surgical techniques, avoiding long time of surgery, reducing the duration of severe hypotension whenever possible and implementing measures to tight control of blood pressure, body temperature and glycaemia could help to decrease the risks of perioperative stroke (Selim M, 2007). Another important question is to avoid stopping previous antithrombotic therapies (antiplatelet drugs or oral anticoagulants) since the discontinuation of these therapies is associated to an increased risk of perioperative stroke (Sibon I and Orgogozo JM, 2004; Maulaz et al., 2005). Some studies have reported the security of the continued use of those treatments in patients that undergo dental procedures, arthrocentesis, cataract surgery, diagnostic endoscope and orthopaedic surgery (Armstrong et al., 2006; Selim M, 2007). On the other hand, it has been recently pointed out that preoperative administration of statins (Durazzo et al., 2004) and beta-blockers (Crystal et al., 2004) could reduce the incidence of stroke after CABG.

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Chapter 47

Rare causes of stroke

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47.1. Systemic disorders predisposing to stroke

A heterogeneous group of non-hereditary systemic disorders shares stroke as a common symptom. The development of disease symptoms in these disorders involves the arterial system, generally in the absence of atherosclerosis and inflammation. Most of pathologies are sporadic with their frequency varying between 1 in 5,000 and 1 in 200,000 patients. Commonly, the skin, ears, or eyes are affected. In very rare conditions all the sensory organs may be involved.

47.1.1. Non-hereditary systemic disorders involving the skin

47.1.1.1. Malignant atrophic papulosis—Kohlmeier–Degos' disease

The first case of malignant atrophic papulosis (MAP) was probably reported by Kohlmeier in 1941, who attributed the cause of skin lesions and gastrointestinal (GI) perforations occurring in a young man to a form of thromboangiitis obliterans (Kohlmeier, 1941). In 1936, Degos examined a patient with the same symptoms and suggested a different entity, which he named "papulosquamous dermatitis" (Degos et al., 1936). Six years later, after the patient's autopsy, the term "malignant atrophic papulosis" was definitively established (Degos et al., 1948). MAP is a rare and clinically distinctive vasculopathy, characterized mainly by cutaneous features with frequent GI involvement. All systems can be affected (Degos et al., 1948), but skin eruption is a constant and pathognomonic sign (Degos, 1979).

MAP is usually fatal, although a few patients with a benign form have been reported (Moulin, 1988; Shimazu et al., 1988). It occurs mainly in young adults but sometimes it may develop during childhood (Horner et al., 1976; Barabino et al., 1990). The condition evolves over several years with the first symptom being general weakness (Lomholt et al., 1968; Horner et al., 1976; Muller and Landry, 1976; Pierce and Smith, 1978; Dastur et al., 1981; Soter et al., 1982; Label et al., 1983; Sotrel et al., 1983; Lee et al., 1984; Sibillat et al., 1986; Doutre et al., 1987; Moulin, 1988; Rosemberg et al., 1988; Shimazu et al., 1988; Barabino et al., 1990; Casparie et al., 1991). Death occurs mainly after GI perforations or involvement of the central nervous system (CNS) (Degos et al., 1948, 1979; Dastur et al., 1981). Although MAP is easily recognizable after clinical examination or pathological study, the etiology is unknown and there are no universally accepted treatment strategies. All organ systems can be involved and in all cases clinical manifestations are a consequence of multifocal infarctions.

The skin is always involved, although symptoms may be absent in the early stages of the disease (Degos, 1979). MAP-associated cutaneous lesions, depending on the stage, are whitish/skin-colored or erythematosus papules with central atrophy, having a porcelain-like appearance. They have a scattered distribution and are disseminated on the trunk and limbs with a size varying between 2 and 5 mm (Fig. 47.1). The eruption is always asymptomatic and evolves within a few days to a central atrophy leaving a flattened center, sharply surrounded by an erythematosus peripheral circle (Fig. 47.2) (Degos et al., 1948, 1979). In some aspects, especially in the early stages, this eruption can resemble the dermatological findings in systemic lupus erythematosus (SLE) (Doutre et al., 1987).

Gastrointestinal lesions are always present in MAP and in most cases are the cause of death (Degos et al.,

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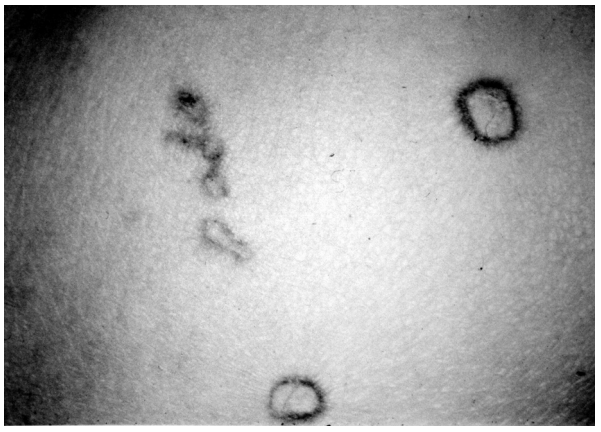

Fig. 47.1. Cutaneous lesions of MAP on trunk and arm in a 35-year-old woman with MAP.

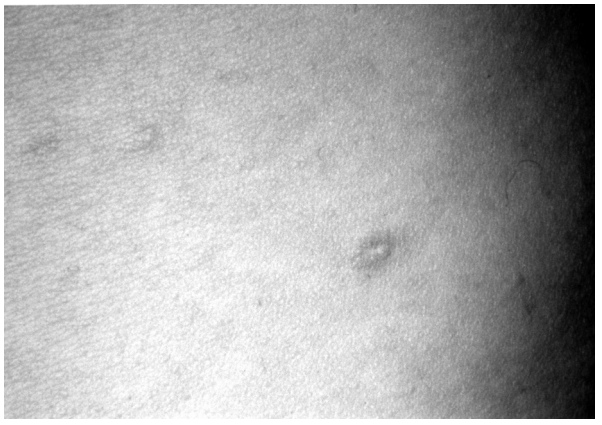

Fig. 47.2. Papules with central atrophy showing porcelain appearance, surrounded by an erythematosus peripheral circle, disseminated on the trunk.

1948, 1979). The first gastrointestinal symptoms are a progression to anorexia, diarrhea, and diffuse abdominal pain (Degos et al., 1936, 1948; Kohlmeier, 1941). Frequently the condition of the patient deteriorates leading to intestinal obstructions and hemorrhages caused by perforations with peritonitis (Degos et al., 1948). The diagnosis can easily be made by endoscopy (Casparie et al., 1991) or laparoscopy (Shimazu et al., 1988) which reveal the same lesions (except larger) as those seen on the skin. Occasionally, perforations can be confined to within the seromuscular wall (Shimazu et al., 1988). Because of the severe consequences of GI involvement, Casparie et al. (1991) have emphasized the importance of routinely performing endoscopy in MAP patients to detect silent or early perforation, even in patients without GI complaints.

Neurological symptoms are mainly due to an involvement of the CNS but a few cases of peripheral neuropathy have been reported. These symptoms may be the primary manifestation of the condition and may precede skin or other systemic symptoms by many years, especially in children (Rosemberg et al., 1988; Barabino et al., 1990). Neurological signs include mental dysfunction, motor and/or sensory deficits, ophthalmoplegia, and cranial nerve dysfunction. The abnormal neurological result of multifocal infarctions or hemorrhages, located in any part of the CNS or peripheral nerves, is a result of small- or medium-sized artery or cerebral vein involvement (Dastur et al., 1981). Peripheral neuropathies, a consequence of demyelination, are rarely encountered (Horner et al., 1976). In 1983, Label et al. studied a patient with MAP who developed a polyradiculopathy with elevated cerebrospinal fluid (CSF) protein and hypoglycorrhachia that was attributed, after autopsy, to multifocal infarctions and necrosis of the CNS and peripheral nerve sheaths. Therefore, MAP should be considered in the differential diagnosis of polyradiculopathy (Muller and Landry, 1976; Label et al., 1983).

Ophthalmologic symptoms are common, being reported in 35 of the 105 published cases. Various eye structures can be involved, predominantly the conjunctiva but also the sclera, retina, choroid, uvea, eyelids, pupils, and optic tracts (Sotrel et al., 1983; Lee et al., 1984; Sibillat et al., 1986). There are anecdotal reports of intra-thoracic (Pierce and Smith, 1978), bladder (Lomholt et al., 1968), and heart involvement (Sotrel et al., 1983).

MAP is an occlusive endarteriopathy that involves small- and middle-sized arteries and veins. The appearance of lesions is similar regardless of the tissue affected and it has been classified as a proliferative vasculopathy (Degos et al., 1948, 1979; Soter et al., 1982). Using refined microscopy, the lesions are characterized by intimal proliferation in the absence of an inflammatory reaction (Su et al., 1985). This process is confined to the intima of the vessel and always spares the media (Demitsu et al., 1992).

Molenaar et al. (1987) identified three lesion stages: early, intermediate and late. Early lesions are a result of cellular proliferation and edema of the intima with evidence of immune complex deposition; thrombosis is occasionally identified and may be attributed to a secondary phenomenon. The intermediate stage is characterized by a decrease in edema and a proliferation of smooth muscle. The late lesions consist of a cellular intimal sclerosis with hyalinization and a narrowing or obliteration of the vascular lumen (Molenaar et al., 1987). Although inflammation is often absent, it can sometimes be identified in the early stages (Demitsu et al., 1992). In subsequent stages the absence of inflammatory cells facilitates the differentiation of

Kohlmeier–Degos' disease from other forms of vasculitis (Su et al., 1985). Electron microscopy confirms the presence of intimal proliferation with vacuolization and edema (Su et al., 1985).

The etiology of MAP remains unknown. Several hypotheses have been proposed but none have been confirmed. A congenital etiology was proposed following the identification of several cases of MAP in one family. In one report, six relatives presented clinical features of MAP (Kisch and Bruynzeel, 1984). A mother and her daughter were shown to be affected in another report (Moulin et al., 1984). In both cases an autosomal dominant mode of inheritance was proposed, but never confirmed. An autoimmune mechanism has also been proposed because dermatological lesions observed in SLE are in some aspects similar to MAP lesions (Black and Hudson, 1976; Doutre et al., 1987). This hypothesis was reinforced by the detection of antiphospholipid antibodies in one MAP patient (Asherson and Cevera, 1993). A strong argument against the autoimmune hypothesis is, however, the absence of inflammatory cells. Further studies are required to confirm or refute these findings. A viral etiology has also been suspected after the detection of virus-like particles in endothelial cells on electron micrographs (Degos et al., 1948, 1979). These findings have not been confirmed and intracytoplasmic particles resembling paramyxovirus have subsequently been found to be the result of cellular degeneration (Stahl et al., 1978; Bioulac et al., 1980).

No treatment is known to be effective. Due to the possible involvement of an autoimmune process, immunosuppressive therapy has been proposed but a benefit has not yet been established (Asherson and Cevera, 1993). Antifibrinolytic agents have been proposed for treatment of early manifestations of artery occlusion but no benefit has been proven (Black and Hudson, 1976). Reports concerning the use of antiplatelet therapy are inconsistent. Several observations have revealed no beneficial effect (Stahl et al., 1978; Pallesen and Rasmussen, 1979), while in 1990 Drucker et al. demonstrated a real benefit in a patient who had several abnormalities of platelet adhesiveness and aggregation. The patient was free of complications during several months of treatment but deteriorated when this was discontinued (McFarland et al., 1978; Tribble et al., 1986; Drucker, 1990). However, this observation must be tempered by the fact that coagulation abnormalities are not a common feature in MAP (Howsden et al., 1976; McFarland et al., 1978; Pallesen and Rasmussen, 1979; Daniel et al., 1982; Tribble et al., 1986; Drucker, 1990). In the acute phase, Degos has proposed anticoagulation with heparin to avoid artery occlusion (Degos, 1979), while surgery has commonly been proposed for the treatment of intestinal perforation (McFarland et al., 1978; Pallesen and Rasmussen, 1979).

47.1.1.2. Diffuse meningocerebral angiomatosis and leukoencephalopathy—Divry–Van Bogaert's syndrome

Diffuse meningocerebral angiomatosis and leukoencephalopathy is a congenital recessive disease that affects both adults and children (Van Bogaert, 1967; Vonsattel and Hedley-Whyte, 1989). This syndrome was first described in 1946 by Divry and Van Bogaert in three brothers with livedo reticularis who gradually developed dementia, seizures, and pyramidal signs approximately 15 years after the initial diagnosis (Van Bogaert, 1967). Autopsy disclosed leptomeningeal angiopathies, brain infarcts, and demyelination (Van Bogaert, 1967).

There are two different forms. The adult form is characterized by skin lesions and neurological disorders. Skin symptoms consist of a diffuse symmetrical livedo reticularis which can increase at the onset of neurological problems. Skin biopsies disclose increased dermal capillaries with focal loss of "zonulae occludens" between endothelial cells. Neurological disorders include seizures, dementia, and motor disturbances, with dementia being the most frequent manifestation (Van Bogaert, 1967). The motor disturbances are related to the presence of brain infarcts. Generally death occurs between 10 and 15 years after the onset of neurological symptoms (Van Bogaert, 1967; Vonsattel and Hedley-Whyte, 1989). In the infantile form the onset of symptoms occurs after the age of 3 years (Van Bogaert, 1967). In one patient a poliomyelitis vaccination was the presumptive cause (Vonsattel and Hedley-Whyte, 1989). Skin anomalies and neurological disorders are characteristic. Skin lesions may be absent in children but when present they do not differ from those observed in the adult form (Van Bogaert, 1967; Vonsattel and Hedley-Whyte, 1989). The neurological signs include seizures and neuropsychomotor involvement. The duration of the disease is shorter when it appears in adults and death generally occurs within the first 24 months after the onset of neurological signs (Van Bogaert, 1967).

Neuropathological abnormalities include brain infarcts, demyelination of white matter, and cerebromeningeal angiomatosis. Cerebromeningeal angiomatosis is a large corticomeningeal network with vascular congestion and multiple vessel occlusions, and is the most constant and pathognomonic finding of this disease (Van Bogaert, 1967; Vonsattel and Hedley-Whyte, 1989). Microscopic examination reveals fibrotic changes of the vascular walls with fatty degeneration

and amyloid deposits. These abnormalities lead to diffuse cerebral infarctions in the gray and white matter. Demyelination of the central white matter is also observed in practically all cases; this consists of axonal and oligodendrocytic loss with astrogliosis (Van Bogaert, 1967; Vonsattel and Hedley-Whyte, 1989). These abnormalities occur predominantly around the vessels.

47.1.1.3. Epidermal nevus syndrome

The epidermal nevus syndrome is a sporadic neurocutaneous disorder characterized by epidermal nevi and congenital anomalies that can involve all systems, frequently the brain (Dobyns and Garg, 1991; Pavone et al., 1991; el-Shanti et al., 1992). Two entities are commonly described. The classic form is characterized by epidermal nevi and brain infarctions. The second form, often called the neurological variant, is characterized by hemimegalencephaly, gyral malformation, mental retardation, seizures and facial hemihypertrophy (Dobyns and Garg, 1991; Pavone et al., 1991; el-Shanti et al., 1992). Of the 70 patients previously described, half were shown to have the hemimegalencephaly variant (Pavone et al., 1991).

Neurological manifestations result from infarcts caused by blood vessel dysplasia. Clinically, this syndrome affects young people and neonates (el-Shanti et al., 1992). In all patients the diagnosis is confirmed by angiography, demonstrating vascular dysplasia consisting of segmental beading and dilatation of cerebral arteries. An increase in vascularity in the capillary field and widening of the posterior portion of the superior sagittal sinus are frequently seen (Dobyns and Garg, 1991). Less often, angiography shows fusiform aneurysms and dilatation of the cavernous part of the carotid arteries (Dobyns and Garg, 1991).

47.1.1.4. Atrial myxoma-lentiginosis

Facial lentiginosis associated with atrial myxoma is a rare cause of stroke (Forney et al., 1966; Carney et al., 1985). The frequency of atrial myxoma is approximately 1/100,000 stroke patients in various autopsy series. A congenital dominant autosomal form has been described in patients associated with lentiginosis and myxoma (Forney et al., 1966; Carney et al., 1985).

Embryologically, it is probably the involvement of the mesodermic structures that leads to the entity described by Forney et al. in 1966. This condition combines facial lentiginosis, mitral insufficiency, myxoma, deafness, and bone abnormalities (Wolpert and Caplan, 1992). Several different patients were reported and, in all instances, cerebral infarction was probably caused by cardiac embolism. Although this syndrome is rare, because of its congenital origin, family members are often studied who may also have cardiac tumors and neoplastic conversion of skin lesions (Forney et al., 1966).

47.1.1.5. Eosinophil-induced neurotoxicity and cerebral infarction

Hypereosinophilia is usually a secondary process in response to allergic and parasitic diseases (Fauci et al., 1982; Dorfman et al., 1983; Weaver et al., 1988). Although there are beneficial effects to tackling the primary disease, eosinophils can exert several non-specific toxic effects with concomitant damage to tissues. Both the central and peripheral nervous systems are frequently affected by this undesirable toxicity (Fauci et al., 1982; Dorfman et al., 1983; Weaver et al., 1988). According to Weaver and colleagues, who described a patient with cerebral involvement due to hypereosinophilic syndrome, the mechanisms of eosinophil-induced neuronal damage are multiple (see Table 47.1). The neurotoxic potential of eosinophil proteins must also be considered.

Three basic proteins have been isolated: medial basic protein, eosinophil cationic protein, and eosinophil-derived neurotoxin (Fauci et al., 1982; Dorfman et al., 1983). Release of medial basic protein can damage endothelial cells and may be the cause of thrombosis and secondary artery-to-artery emboli (Dorfman et al., 1983; Weaver et al., 1988). Eosinophil cationic protein may potentiate a hypercoagulable state and contribute to a thrombotic tendency. Eosinophil-derived neurotoxin has a direct toxic action on neuronal tissue and myelinated axons. The three major clinical pictures of eosinophil-induced neurotoxicity are axonal peripheral neuropathy, dementia, and stroke (Dorfman et al., 1983; Weaver et al., 1988).

Cerebral infarction is secondary to medial basic protein-mediated endothelial damage, eosinophil cationic protein-mediated hypercoagulability and eosinophil-

Table 47.1

Mechanisms of eosinophil-induced neurotoxicity

Direct neural tissue infiltration.
Damage related to eosinophil function, either by direct cytotoxicity or by antibody dependent cellular cytotoxicity
Damage related to eosinophil products, either by secretion into neurons or by secretion of intracytoplasmic granules contained in the circulation, with subsequent damage to neural tissue
Embolic cerebral infarction related either to thrombus or generalized hypercoagulable state
Nervous system damage secondary to eosinophil mediated action in remote organ systems

mediated cardiopathy. Weaver et al. (1988) reported a patient with a left occipital cerebral infarction that was followed 3 months later by a right parietal cerebral infarction. Dementia developed 1 year later and a neurophysiological study showed a polyneuropathy. Management consists of the treatment of hypereosinophilia with prednisone and hydroxyurea. Weaver et al. have recommended anticoagulation in preference to antiplatelet therapy for the treatment of embolic cerebral infarctions (Weaver et al., 1988).

47.1.1.6. Kawasaki syndrome

The "mucocutaneous lymph node syndrome" was first described by Kawasaki in 1967 and presents as an acute febrile exanthematous disease. The initial observation described the medical evolution of several Japanese children who presented with symptoms of fever and maculo-papular skin involvement (Fig. 47.3). More recent literature has confirmed that Kawasaki syndrome is found exclusively in children and young adults (Kawasaki, 1967; Lauret et al., 1979; Marcella et al., 1983; Boespflug et al., 1984; Lapointe et al., 1984; Laxer et al., 1984; Yonesaka et al., 1992). The involvement of skin and all mucous membranes is characteristic of the disease (Kawasaki, 1967) and the course always follows the same pattern. All patients have fever at onset followed within the first 3 days by the development of squamous skin, generalized erythema, sometimes with peeling exanthema, conjunctivitis, and generalized lymph nodes—all the signs resembling those encountered in scarlet fever (Kawasaki, 1967). The skin of the trunk is more frequently affected than other areas. Following these symptoms, systemic generalization can occur, essentially due to multiple artery involvement. Most patients have spontaneous lesion regression but some can suffer stroke, subarachnoid hemorrhage, or myocardial infarction. The etiological basis of this disease remains unknown and consequently a treatment strategy has not yet been established.

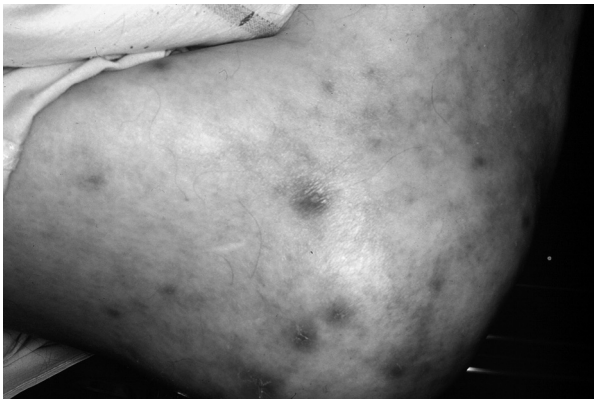

Fig. 47.3. Arm papular eruption in a 12-year-old boy with Kawazaki's disease.

Roughly 1.5–2% of patients will develop vascular involvement within a month. This may be due to either coronary or circle of Willis aneurysms leading to severe or even lethal complications (Laxer et al., 1984). The most frequent complications previously described are myocardial infarctions which are attributed to progressive occlusion of coronary arteries (Yonesaka et al., 1992).

The mechanism by which stroke can occur is twofold. It may be a consequence of middle- or small-size cerebral artery thrombosis or single multiple emboli arising from a cardiac source. In most of the cases previously described this is caused by cardiac akinesia following myocardial infarction or by transient episodes of atrial fibrillation. Alternatively, it may be a consequence of recent myocardial infarction. Asymptomatic cerebral infarction has also been reported both in patients with skin and mucous membrane involvement only and in patients with cardiac dysfunction due to coronary artery occlusion. Neurological signs include mental dysfunction, motor and/or sensory deficits, ophthalmoplegia and cranial nerve dysfunction. The neurological abnormalities result in multifocal infarctions or hemorrhages and are located in any part of the CNS (Kawasaki, 1967; Lauret et al., 1979; Marcella et al., 1983; Boespflug et al., 1984; Lapointe et al., 1984; Laxer et al., 1984; Yonesaka et al., 1992).

Since Kawasaki's disease can affect all organs it has been regarded as a pan-arteritis with involvement of medium- and small-sized arteries. Large-artery involvement is exceptional since only one case of carotid involvement has been reported (Lauret et al., 1979). The disease mechanism remains unknown. Kawaski's disease has been classified as a proliferative vasculopathy, and associated lesions are characterized by intimal proliferation in the absence of an inflammatory reaction. Angiitis of coronary arteries is the most frequent finding but cerebral arteries can also be affected. Pathologically, involvement of both artery intima and media is encountered (Marcella et al., 1983; Boespflug et al., 1984; Yonesaka et al., 1992). Early lesions consist of intimal proliferation accompanied by a slight edema, without evidence of immune complex deposition. The second stage is marked by the formation of aneurysms due to rupture of both intima and media layers. The third stage is an occlusive endarteriolopathy, favored in the late stages by an increase in platelet aggregation and adhesiveness. The late lesion consists of an acellular intimal sclerosis with hyalinization and narrowing or obliteration of the vascular lumen. Mild inflammation can sometimes be

found in the early stages. Pathological examination of eye and mouth mucous membrane or skin lesions provides no evidence of viral inclusion or the presence of bacteria. An autoimmune mechanism has been advocated but the absence of an increase in antibody levels and lymphocytic infiltration do not support this hypothesis (Lauret et al., 1979; Laxer et al., 1984; Yonesaka et al., 1992).

At present there is no known successful treatment. Antiplatelet therapy could be useful for the treatment of secondary occlusions as these are thought to be caused by an increase in platelet aggregation and adhesion. Reports concerning the use of antiplatelet therapy are, however, inconsistent. Since aneurysm development is one of the major symptoms of the disease, careful thought should be given to the type of medication that is administered bearing in mind the risk of brain hemorrhage (Boespflug et al., 1984).

47.1.2. Non-hereditary systemic disorders involving the eyes

47.1.2.1. Eales' disease

Eales' disease was first described in 1882 as a rare, idiopathic condition, encountered mainly in young males (Gordon et al., 1988). It is a type of retinal peri-vasculitis characterized by frequent recurrent retinal and vitreous hemorrhages (Gordon et al., 1988; Gadkari et al., 1992). Occasionally, small- and medium-sized arteries of the CNS can be involved and this non-inflammatory perivasculitis leads to artery occlusion (Atabay et al., 1992; Sen et al., 1992; Weber and Conrad, 1993). Other systems can be involved, such as the gastrointestinal tract or spinal cord (Phanthumchinda, 1992; Pomonis et al., 1992).

Pathologically, it is an involvement of medium- and small-sized arteries with lymphocyte infiltration of the media, without inflammatory changes (Gadkari et al., 1992; Weber and Conrad, 1993). However, when studying 27 patients with peripheral retinal vasculitis due to Eales' disease, Sen et al. (1992) observed an increase in serum alpha-1 acid glycoprotein levels with both moderate and severe forms of the disease. This suggests that this condition could have an immune-mediated origin (Weber and Conrad, 1993). Anticoagulation or antiplatelet therapy are the current treatments of choice. Immunosuppressive therapy should also be considered in patients with moderate and severe forms of Eales' disease.

47.1.2.2. Acute posterior multifocal placoid pigment epitheliopathy

Acute posterior multifocal placoid pigment epitheliopathy (APMPPE) was first described by Gass in 1968. The disease is characterized by a sudden bilateral blurring of vision associated with multifocal yellowish-white placoid lesions of the retinal pigment epithelium (Gass, 1968; Deutman et al., 1972; Stoll et al., 1991). The acute onset of blurred vision in a young adult with typical lesions in the posterior retinal pole is characteristic of APMPPE (Gass, 1968). The age of patients with APMPPE ranges from 15 to 40 years. Both sexes are affected and the disease is observed in different races.

The primary lesion affects the small choroidal arterioles, leading to ischemia of the retinal pigment epithelium (Gass, 1968). APMPPE can follow a viral-like illness of the respiratory or digestive tracts (Gass, 1968; Deutman et al., 1972; Azar et al., 1975; Stoll et al., 1991). In one patient, an adenovirus type-5 infection was detected, the virus was isolated from a throat swab and the antibody titer was raised in serum (Gass, 1968). The visual form is the most common type (Smith et al., 1983; Manto et al., 1995). Persistent scotomas have been described but the visual outcome is generally good. The ocular involvement may be complicated by episcleritis and keratitis, iridocyclitis and retinal vasculitis (Holt et al., 1976; Jacklin, 1977; Smith et al., 1983; Lyness and Bird, 1984).

As well as the eyes, the CNS is often involved in APMPPE (Holt et al., 1976; Bullock and Fletcher, 1977; Fishman et al., 1977; Jacklin, 1977; Priluck et al., 1981; Smith et al., 1983; Lyness and Bird, 1984; Kersten et al., 1987; Laatikainen and Immonen, 1988; Wilson et al., 1988; Bewermeyer et al., 1993). Neurological signs include severe headache, neck stiffness, and stroke (Deutman et al., 1972; Bullock and Fletcher, 1977; Smith et al., 1983; Stoll et al., 1991). Cerebral vasculitis is also a complication, occurring either simultaneously or after the ocular signs (Bullock and Fletcher, 1977; Fishman et al., 1977; Wilson et al., 1988; Stoll et al., 1991). In addition, several observations indicate that APMPPE may be a manifestation of an autoimmune disease such as erythema nodosum, thyroiditis, Crohn's disease, giant cell arteritis or acute nephritis (Deutman et al., 1972; Holt et al., 1976; Bullock and Fletcher, 1977; Jacklin, 1977; Priluck et al., 1981; Laatikainen and Immonen, 1988). Frequently, aseptic meningitis can precede the blurring of vision (Manto et al., 1995). CSF analysis shows lymphocytic pleocytosis and elevated protein levels. Oligoclonal bands of CSF proteins are occasionally present (Azar et al., 1975; Jacklin, 1977; Smith et al., 1983; Manto et al., 1995). The pathogenesis of APMPPE remains unknown. Lyness and Bird have speculated that the pathogenic mechanism could be hypersensitivity to tetracycline, sulfamethoxazole and trimethoprim (Lyness and Bird, 1984).

Treatment with steroids is followed by a rapid improvement in neurological signs (Deutman et al., 1972; Manto et al., 1995). Recurrences could happen and cerebral infarction sometimes develops when lowering steroid doses (Smith et al., 1983; Kersten et al., 1987). Long-term immunosuppression with aziathoprine has been proposed but the data are insufficient to accept this as a treatment strategy (Stoll et al., 1991; Bewermeyer et al., 1993).

47.1.3. Non-hereditary systemic disorders involving the ears and eyes

47.1.3.1. Retinocochleocerebral arteriolopathy—Susac's syndrome

The retinocochleocerebral arteriolopathy is a diffuse encephalopathy with retinal vascular occlusions, hearing loss and absence of systemic disease. It was first described by Susac et al. in 1979 in two women with obvious psychiatric symptoms. Both also had retinal artery occlusions and hearing loss. The cognitive signs were predominant and consisted of progressive memory troubles and abulia. Multiple retinal artery occlusions result in blindness.

Bogousslavsky and Caplan have together described several patients with this syndrome. In all subjects, laboratory tests were unremarkable with the exception of a few patients who showed a slight increase in sedimentation rate, the presence of antinuclear antibodies at low titer, and an increase in CSF protein content (Bogousslavsky et al., 1989).

Generally, segmental narrowing and the involvement of small pial and cortical vessels are disclosed by angiography. In one case, biopsy revealed "healed angiitis." Bogousslavsky has suggested the use of immunosuppressive therapy, based on the observation that anomalies of lymphocyte T-cell helpers and suppressors were evident in his patients. One patient improved under this treatment but the condition of another deteriorated (Bogousslavsky et al., 1989). Currently, steroid treatment is recommended in the acute phase but a benefit from prolonged immunosuppression has not yet been established (Heiskala et al., 1988).

47.2. Cerebral angiopathies predisposing to stroke

The conditions described in this chapter represent a heterogeneous group of vasculopathies. These diseases are very rare and account for between 1 in 50,000 and 1 in 350,000 of stroke patients. In terms of a percentage of the total number of strokes, their contribution is very small.

47.2.1. Fibromuscular dysplasia

Fibromuscular dysplasia (FMD) is an arteriopathy occurring predominantly in Caucasian women. The most common age of diagnosis is between 30 and 50 years. It is the most frequently recognized arterial dysplasia, representing approximately 1% of autopsy and angiography series (Sandmann et al., 1992). The renal, splanchnic, and cervico-cranial arteries are most commonly involved, with the disease having a preference for middle-sized vessels. FMD is preferentially located in the distal two-thirds of the renal arteries and segments of the distal extracranial vertebral and carotid arteries adjacent to the second cervical vertebra (Edwards et al., 1992; Josien, 1992; Sandmann et al., 1992; Velkey et al., 1992; Watanabe et al., 1993) (Fig. 47.4). Occasionally, the cavernous part of the carotid arteries and the arteries of the circle of Willis may be involved.

Pathologically, the medial layer is most commonly affected but all layers of the arterial wall can be involved (Sandmann et al., 1992; Velkey et al., 1992). The pathological process consists of fibrodysplasia of smooth muscles leading to the formation of rings of fibrous tissue and smooth muscle. These rings alternate with areas of medial thickening and destruction of the elastic layer, leading to alternate narrowing and widening of the arterial lumen. Occasionally, the intimal region is involved causing proliferation of fibrous cells, which results in a narrowing of the

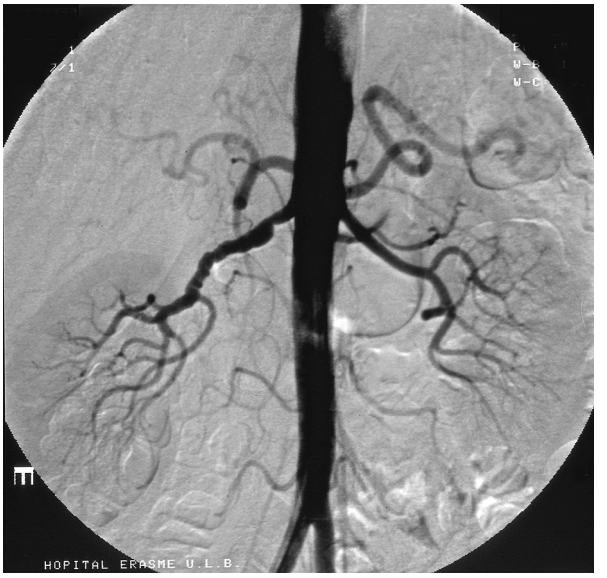

Fig. 47.4. Typical "string of beads" and arterial stenosis of right renal artery in the same patient. Arterial hypertension was attributed to the renal artery stenosis.

lumen. This less common type of FMD is mainly found in children and young adults (Sandmann et al., 1992).

The typical appearance is alternating zones of widening and narrowing of the arterial lumen leading to the classic "string of beads" pattern (Heiserman et al., 1992; Sandmann et al., 1992). Less frequent features are tubular stenosis, a diverticular appearance or aneurysmal dilatation. Diagnosis is practically always made by angiography but it can be confirmed by duplex imaging of the extracranial carotid and vertebral arteries or transcranial Doppler (Giller et al., 1992; Heiserman et al., 1992). Magnetic resonance angiography (MRA) can also be used (Ashleigh et al., 1992; Nishiyama et al., 1992; Schulze et al., 1992). The use of MRA may avoid the need for conventional arteriography in patients suspected of having FMD after duplex examination.

The mechanism by which FMD causes stroke is unclear; the prevalence of cigarette smoking and the use of contraceptive therapy have been proposed to explain the female predominance. Although the relationship between stroke and FMD remains questionable (Sandmann et al., 1992; Schulze et al., 1992; Velkey et al., 1992) some mechanisms have been proposed such as: (1) artery-to-artery emboli; (2) local thrombosis; (3) emboli arising from a diverticulum; or (4) emboli arising from a pseudo-aneurysmal sac. A frequent cause of stroke in FMD patients does, however, appear to be spontaneous artery dissection (Bour et al., 1992; Edwards et al., 1992; Gatalica et al., 1992; Nishiyama et al., 1992; Baumgartner and Waespe, 1993). The association of atherosclerosis and FMD is also frequent but it is uncertain how much the primary condition favors the development of atheromatous disease (Ashleigh et al., 1992; Bour et al., 1992; Gatalica et al., 1992; Nishiyama et al., 1992; Sandmann et al., 1992; Baumgartner and Waespe, 1993).

Currently, there are no known treatment strategies for FMD. Antiplatelet therapy has generally been proposed (Sandmann et al., 1992). Anticoagulants are not recommended because of the risk of bleeding in the presence of cerebral aneurysms (Gatalica et al., 1992; Nishiyama et al., 1992; Baumgartner and Waespe, 1993). Several surgical procedures have been proposed but thrombo-endarterectomy should only be considered for treatment of symptomatic carotid stenosis (Bour et al., 1992). Some endovascular radiologists recommend angioplasty when the carotid or vertebral are involved; this procedure should, however, be proposed with caution because it may favor arterial dissection, a frequent complication of FMD (Gatalica et al., 1992; Sandmann et al., 1992; Baumgartner and Waespe, 1993).

47.2.2. Primitive arteries

In the very early stages of human embryonic life, various anastomotic channels exist into and between the carotid and vertebrobasilar systems. They are normally present during the first stages of life only to disappear when the embryo is approximately 12–14 mm long (Padget, 1954; Taptas and Katsiotis, 1968; Anderson and Sondheimer, 1976; Lasjaunias and Berenstein, 1987; Parenti et al., 1992; Bahsi et al., 1993; Kindl et al., 1993; Nakai et al., 1993). These anastomotic channels are known as the persistent primitive trigeminal, hypoglossal, otic, and proatlantal arteries (Padget, 1954). They were first named by Padget in 1953 (Padget, 1954) and reviewed by Lasjaunias et al. in 1987 (Lasjaunias and Berenstein, 1987). Occasionally, some of these channels fail to regress and they persist into adult life (Padget, 1954; Bahsi et al., 1993).

Occlusion of these arteries, when they persist, can lead to cerebral infarctions. In 1993, Bahsi et al. described the case of a 55-year-old woman admitted to hospital with loss of consciousness due to bilateral mesencephalic and thalamic infarctions (Bahsi et al., 1993). She was identified as having a top-of-the-basilar syndrome. Other rare cases of ischemic stroke in the carotid territory have also been described after occlusion of the persistent trigeminal artery (a collateral of the basilar artery which reaches the internal carotid artery near the base of the skull) (Padget, 1954; Taptas and Katsiotis, 1968; Anderson and Sondheimer, 1976; Lasjaunias and Berenstein, 1987; Parenti et al., 1992; Bahsi et al., 1993; Kindl et al., 1993; Nakai et al., 1993). Anastomotic vessel occlusions are caused by either cerebral emboli or more frequently local thrombosis (Padget, 1954; Taptas and Katsiotis, 1968; Anderson and Sondheimer, 1976; Lasjaunias and Berenstein, 1987; Parenti et al., 1992; Bahsi et al., 1993; Kindl et al., 1993; Nakai et al., 1993).

47.3. Cerebral aneurysms

Strokes secondary to subarachnoid hemorrhage result mainly from vasospasm of the major cerebral arteries. However, other mechanisms such as aneurysm-to-artery emboli are possible when aneurysmal sacs are greater than 25 mm (Taptas and Katsiotis, 1968; Sandmann et al., 1992). In the presence of these giant cerebral aneurysms, ischemic stroke caused by emboli arising from the sac can occur. This clinical finding is rare but has to be considered in selected patients in whom no other cause of stroke has been identified. The first observation was made by Taptas and Katsiotis (1968) who reported a patient who had a stroke after a subarachnoid hemorrhage and in whom angiography did not

demonstrate vasospasm (Taptas and Katsiotis, 1968). A subsequent follow-up revealed that stroke was the consequence of an aneurysm to artery embolus.

Four criteria have been proposed to define the etiology of cerebral aneurysm: (1) the presence of transient ischemic attacks (TIA) or stroke; (2) the presence of a thrombus in the aneurysmal sac; (3) the absence of other sources of emboli; and (4) the absence of vasospasm (determined by cerebral angiography) (Lomholt et al., 1968). Currently, the best techniques for diagnosis of this disease are magnetic resonance imaging (MRI), which can image partially or total thrombosed aneurysms, and transcranial Doppler, which can provide information about the presence of associated vasospasm (Taptas and Katsiotis, 1968; Lasjaunias and Berenstein, 1987; Kindl et al., 1993). Histologically, there is a good correlation between the size of the aneurysm sac and the incidence of saccular thrombosis; the larger the aneurysm the greater the risk of an intra-aneurysmal thrombus (Taptas and Katsiotis, 1968; Lasjaunias and Berenstein, 1987; Murros and Toole, 1989; Kindl et al., 1993; Nakai et al., 1993). Stroke can occur before or intra-operatively.

Cerebral aneurysms are treated by surgery. The surgical dissection must be precise to avoid secondary emboli. In patients where surgery is not an option, preventive treatments are still discussed; for example, the use of anticoagulants which can avoid thrombus formation, but these treatments may promote fatal subarachnoid hemorrhages.

47.4. Radiation-induced angiopathy

The adverse effects of radiation on blood vessels have been known since the end of the nineteenth century. Arteries, both extracranial and intracranial, and veins have been shown to be involved (Lambrechts and de Boer, 1965; Levinson et al., 1973). Radiation-induced arteriopathy is a result of therapeutic irradiation of neck tumors such as lymphomas, thyroid tumors, or intracranial tumors such as optic tract gliomas.

Pathologically, arterial lesions caused by radiation have been studied in both animal and human models. In animal models, Lambrechts and de Boer (1965) showed that a five gray irradiation induces extensive changes in small and middle-sized arteries, in hypercholesterolemic rabbits (Lambrechts and de Boer, 1965). These changes are: (1) penetration of fat into the arterial walls; (2) deposition of lipophages; (3) formation of atherosclerotic plaques in the intima; and (4) structural changes in the elastic fibers. They concluded that radiation primarily affects the endothelial cells and they emphasized the role of a high cholesterol diet, which activates lysosomal enzymes and favors infiltration of lipid droplets beneath the endothelium (Glick, 1972). Further studies using electron microscopy have demonstrated extensive changes in the endothelium. Adventitial lesions are caused by involvement of the vaso-vasorum (Levinson et al., 1973).

Extrapolation to human arteries is difficult but autopsy examinations have disclosed vacuolization and thickening of the intima, changes in the elastic fibers, and degeneration of the endothelial cells by the same process seen in animal models (Lambrechts and de Boer, 1965; Levinson et al., 1973). Electron microscopy has disclosed swelling and detachment of endothelial cells with a splitting of the basement membrane. It has also disclosed subintimal foam cells which closely resemble circulating lipid-laden macrophages, leading to the production of atherosclerotic-like lesions. Clinically, subintimal foam cells in medium- and small-sized vessels are a diagnostic feature of radiation therapy (Levinson et al., 1973).

Large vessels such as the carotid or vertebral arteries are less affected by x-ray therapy. However, there have been some reports of rupture of the internal carotid artery after subclavian x-ray (Lambrechts and de Boer, 1965). Autopsy studies have disclosed intimal necrosis, infiltration of leukocytes and fragmentation of elastic fibers. In addition, Glick (1972) demonstrated an accumulation of fat-laden macrophages in the arterial media with atheromatous proliferation and calcification of the intima (Weibel and Fields, 1965). A few studies have reported the effect of x-ray therapy in large intracranial arteries with the same pathological process being demonstrated.

Clinically, the adverse effects of therapy can be observed between 1 week and several decades after radiation (Lambrechts and de Boer, 1965; Weibel and Fields, 1965; Glick, 1972; Levinson et al., 1973). Very early manifestations are rare and generally due to skin necrosis and infection of surgical wounds. Delayed complications are more frequent and occur from 6 month to 10 years (median of 2 years) after treatment. The main symptom is skin radionecrosis (Lambrechts and de Boer, 1965; Weibel and Fields, 1965; Glick, 1972; Levinson et al., 1973), and cerebral angiography frequently discloses arterial stenosis within the radiated area. The interval from irradiation to symptomatic cerebrovascular events is directly related to the size of the irradiated arteries; the larger the vessel the longer the time interval.

47.5. Kinking, coiling, hypoplasia, and dolichoectasia of the cervical arteries

Kinking or coiling of the cervical and cerebral arteries can be observed in both the carotid and vertebral

systems. The origin of these anomalies is probably congenital (Rubanyi, 1991; Brachlow et al., 1992). In most patients, kinkings have been discovered after angiography but Doppler ultrasonography with frequency analysis and B-mode imaging can also be used for diagnosis when the cervical arteries are involved. Kinking or coiling rarely induces symptoms or occlusive disease but may induce TIA or stroke in the case of permanent head rotation during surgical procedure. Brachlow et al. (1992) reported the incidence of a fatal intra-operative cerebral ischemia caused by kinking of the internal carotid artery (Rubanyi, 1991). In other conditions, these anomalies are fortuitous and in stroke patients they are rarely related to the cerebrovascular event (Rubanyi, 1991; Brachlow et al., 1992).

Congenital hypoplasia is a rare condition. It is defined by segmental narrowing of the carotid or vertebral artery, practically always associated with intracranial aneurysm, anomalies of the circle of Willis vessels or intracranial–extracranial physiological bypass (Brachlow et al., 1992). Angiography has disclosed a sudden narrowing of the internal carotid artery just after the primitive division (Sandmann et al., 1992). Differential diagnosis from arterial dissection is difficult but computed tomography (CT) scan of the skull base disclosed in carotid hypoplasia a small carotid canal that allows us to tell the difference between both pathologies.

Dolichoectasia of cervical and cerebral arteries consists of segmental narrowing, widening, and lengthening of arteries of both the vertebrobasilar and carotid systems. Arteries of all sizes can be affected, alone or in combination with others. Histologically, a thinning down of the arterial wall, due to a rarefaction of the elastic layer, associated with a transformation of the media in a fibrous tissue is observed. Atherosclerosis, the consequence but not the cause of these changes, can be observed in such arteries (Padget, 1954; Lambrechts and de Boer, 1965; Weibel and Fields, 1965; Taptas and Katsiotis, 1968; Glick, 1972; Levinson et al., 1973; Anderson and Sondheimer, 1976; Lasjaunias and Berenstein, 1987; Murros and Toole, 1989; Ashleigh et al., 1992; Bour et al., 1992; Brachlow et al., 1992; Edwards et al., 1992; Gatalica et al., 1992; Giller et al., 1992; Heiserman et al., 1992; Josien, 1992; Nishiyama et al., 1992; Parenti et al., 1992; Sandmann et al., 1992; Schulze et al., 1992; Velkey et al., 1992; Bahsi et al., 1993; Baumgartner and Waespe, 1993; Kindl et al., 1993; Nakai et al., 1993; Watanabe et al., 1993). Other vascular malformations can be present such as: cerebral saccular aneurysms, aortic aneurysms, or carotid hypoplasia (Rubanyi, 1991; Brachlow et al., 1992; Sandmann et al., 1992). Individuals between the ages of 50 and 60 years are more frequently affected and a male predominance has been observed.

The consequence of this process can be cerebral infarction due to either artery emboli or occlusion of small arteries. Cranial nerve compressions at the base of the skull can be the consequence of a dolichoectasic artery. Subarachnoidal hemorrhages are rare but can occur when the dolichoectasic artery ruptures (Padget, 1954; Lambrechts and de Boer, 1965; Weibel and Fields, 1965; Taptas and Katsiotis, 1968; Glick, 1972; Levinson et al., 1973; Anderson and Sondheimer, 1976; Lasjaunias and Berenstein, 1987; Murros and Toole, 1989; Ashleigh et al., 1992; Bour et al., 1992; Brachlow et al., 1992; Edwards et al., 1992; Gatalica et al., 1992; Giller et al., 1992; Heiserman et al., 1992; Josien, 1992; Nishiyama et al., 1992; Parenti et al., 1992; Sandmann et al., 1992; Schulze et al., 1992; Velkey et al., 1992; Bahsi et al., 1993; Baumgartner and Waespe, 1993; Kindl et al., 1993; Nakai et al., 1993; Watanabe et al., 1993). Diagnosis is often made by chance in a routine CT scan or MRI. It is confirmed by angiography which discloses a lengthening of the artery.

47.6. Reversible vasoconstriction

Reversible cerebral angiopathy is characterized by the presence of multiple reversible segmental narrowings (Rubanyi, 1991). The existence of this disease and the relationship with the neurological deficit it may cause is still a matter of discussion (Call et al., 1988; Rubanyi, 1991). Two forms have currently been identified. The first form is a consequence of the use of sympathomimetic drugs such as ergot derivatives, after crack-cocaine abuse and as a result of methylamphetamine and phenylpropanolamine administration (Michel et al., 1985; Gautier, 1988; Le Coz et al., 1988; Rothrock et al., 1988; Janssens et al., 1995). The second form is idiopathic, the so-called Call's syndrome or postpartum cerebral angiopathy (Michel et al., 1985; Brick, 1988; Call et al., 1988; Gautier, 1988; Le Coz et al., 1988; Rothrock et al., 1988; Bogousslavsky et al., 1989; Rubanyi, 1991; Raroque et al., 1993; Janssens et al., 1995). In this form vasoconstriction is spontaneous and it occurs predominantly in adults with no associated risk factors for stroke (Le Coz et al., 1988; Bogousslavsky et al., 1989; Rubanyi, 1991). It is more common in women, especially in the puerperum or at the menopause; many of them have a history of migraine (Brick, 1988; Raroque et al., 1993). The pathophysiology and cause of reversible angiopathy are focal arterial vasoconstriction. Reversible cerebral angiopathy has also been recognized following subarachnoid hemor-

rhage due to a ruptured saccular aneurysm or caused by surgical manipulation.

In all patients, neurological deficits are always preceded by high-intensity headaches, nausea and vomiting, mimicking the symptoms found in classic migraine or subarachnoidal hemorrhage (Michel et al., 1985; Brick, 1988; Call et al., 1988; Gautier, 1988; Le Coz et al., 1988; Rothrock et al., 1988; Bogousslavsky et al., 1989; Rubanyi, 1991; Brachlow et al., 1992; Janssens et al., 1995). Less often patients can have epileptic seizures at onset (Brick, 1988). Frequently, neurological deficit is transient, lasting from 7 days to 6 months, but a few patients remain severely handicapped or even die. Cerebral hemorrhage can occur, related to reperfusion, and in some patients brain edema is present.

The classic pattern is the presence, on cerebral angiography, of multiple narrowings of the arteries arising from the circle of Willis which generally disappear within a few days or several months after onset (Brick, 1988). Transcranial Doppler can be useful for the follow-up and the assessment of vasospasm (Bogousslavsky et al., 1989). Cerebrospinal fluid (CSF) examination is often normal and occasionally a mild pleiocytosis may be disclosed (Bogousslavsky et al., 1989; Rubanyi, 1991).

The pathological process involved remains unclear, although severe acute arterial hypertension at onset has been proposed as the cause of an inappropriate arterial vasoconstriction in several cases (Brick, 1988; Smadja et al., 1991; Raroque et al., 1993). As there is uncertainty regarding the pathology, there is no treatment for the acute phase of the disease, except symptomatic treatment for headache, nausea, and vomiting (Raroque et al., 1993).

47.7. Endovascular lymphoma

Also named angiotrophic large cell lymphoma or malignant angioendotheliomatosis, endovascular lymphoma is a rare arteriopathy which is virtually always lethal. It has a particular predilection for small- and middle-size vessels, mainly of the lung, but can involve all organs such as the central nervous system (CNS), lymphatic system, skin, spleen, and bone marrow (Smadja et al., 1991; Wick and Mills, 1991). Small- and middle-size vessels, either arteries or veins, are exclusively involved in endovascular proliferation leading to widening, narrowing and vessel occlusions with extravasation of tumor cells (Dobyns and Garg, 1991). Neoplastic large lymphoid cells are confined to the intravascular compartment and create, in the lung, a pattern akin to cellular interstitial pneumonia (Yousem and Colby, 1990; Delplace et al., 1995). Genotypic and immunohistochemical studies and an atypical cytology with frequent involvement of the CNS, confirms its inclusion within the group of pulmonary lymphomas (Smadja et al., 1991; Delplace et al., 1995). Immunohistochemical studies always disclose an endothelial infiltration of B lymphocytes with a positive reaction for CD-20, CD-45 and CD-75 IgG antibodies. T-lymphocyte infiltration has been reported only in rare cases.

About 1 in 5,000 ischemic strokes are a consequence of this rare arteriopathy. At presentation, patients demonstrate fever, dyspnea, cough, hypoxemia, and signs of CNS involvement such as paresis and frequently obtundation. Brain CT or MRI scans disclose small subcortical infarctions (el-Shanti et al., 1992), while a chest x-ray reveals bilateral fine linear infiltrates. Prognosis is extremely poor, although sporadic responses to steroids have been observed (Yousem and Colby, 1990; Smadja et al., 1991; Wick and Mills, 1991; Delplace et al., 1995).

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