Disorders of the Cerebrovascular System

9

A 65-year old previously healthy man who did not have a regular internist suddenly developed weakness and sensory loss in his right arm, leg, and face and also faced difficulty in speaking. He could understand his wife and knew what he wanted to say but could not get the words out. The episode lasted 20 min and spontaneously ended. He went to the emergency room (ER) where his neurologic examination was normal. He was diagnosed with a transient ischemic attack. The next day his echocardiogram was normal but the carotid artery Doppler ultrasound demonstrated that his left internal carotid artery narrowed by 85%. In addition, the ER also found him to have several risk factors for transient ischemic attack (TIA) including being overweight by 45 lbs, an elevated blood pressure of 160/108, and a hemoglobin A1C of 8.6%. The same day he met an internist to begin medical management for his hypertension, diabetes mellitus, and obesity plus a surgical referral to consider an elective carotid endarterectomy.

Overview

Stroke is a general term that implies damage to cerebral tissue from abnormalities of blood supply. In simple terms there may be insufficient blood supply to the brain (ischemic stroke or infarction), abnormal excess blood (hemorrhagic stroke or cerebral hemorrhage), or inadequate venous drainage of cerebral blood (venous stroke). Ischemic strokes represent 85% of all strokes, hemorrhagic strokes 14%, and venous strokes 1% (Table 9.1).

Stroke is the third leading cause of death in the USA. Each year 800,000 people in the USA develop stroke and 175,000 die. Fortunately, since 1960 the incidence of strokes in the USA has significantly fallen by 50% primarily due to better control of hypertension, diabetes mellitus, and smoking but still 4 million adults in the USA are found to have stroke with an overall stroke prevalence of 750 per 100,000.

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Ischemic Stroke

Introduction

Ischemic stroke occurs from lack of sufficient arterial blood flow in the territory of a specific cerebral artery to maintain neuronal viability. The stroke can be due to (1) intrinsic vascular occlusion (thrombus) that occurs in the neck portion of the internal carotid, vertebral artery, or a cerebral artery or (2) vascular occlusion with

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Table 9.1 Major stroke types[a]

Stroke type	Overall percentage (% of each category)
Ischemic	85%
Carotid artery circulation	(55%)
Vertebral/basilar artery circulation	(12%)
Lacune	(31%)
Other (vasculopathy, coagulopathy, sickle cell, hyperviscosity, vasculitis)	(2%)
Hemorrhagic	14%
Hypertensive hemorrhage	(50%)
Saccular aneurysm	(30%)
Amyloid angiopathy hemorrhage	(15%)
Arteriovenous malformation	(3%)
Other (infective aneurysm, cocaine, anticoagulants)	(2%)
Venous	1%
Thrombosis of cortical veins, deep cerebral veins, or dural sinuses	(100%)

[a]Excludes stroke due to head trauma and subdural hematomas (see Chap. 18 on Traumatic Brain Injury and Subdural Hematoma)

material originating elsewhere (embolism) such as a stenotic site of the internal carotid or vertebral artery or from the heart. The large majority of emboli are blood clots but occasionally they can be air, fat, or tissue fragments. Eighty percent of ischemic strokes involve the carotid artery territory or anterior circulation and 20% involve the vertebrobasilar artery or posterior circulation.

The cause of a stroke depends on the patient's age. In children, congenital heart disease with paradoxical embolism, Moyamoya disease, bacterial endocarditis, rheumatic fever, sickle cell anemia, and mitochondrial disorders should be considered. In young adults, estrogen-related stroke, migraine, vascular malformation, arteritis, hypercoagulation abnormalities, arterial dissections, and drug reactions from amphetamines, heroin, and cocaine may be seen. In middle age, hypertensive hemorrhage, ruptured saccular aneurysm, fibromuscular dysplasia and cardiogenic embolism often occur. The elderly often develop lacunar strokes, multi-infarct dementia, and atherosclerotic thrombotic strokes.

Table 9.2 lists the major modifiable and unmodifiable risk factors for stroke.

Pathophysiology

Cerebral ischemia occurs from inadequate cerebral blood flow to the brain area. Total lack of oxygen and glucose to all brain neurons, as in a 12 to 15 s cardiac arrest, suppresses electrical activity and causes loss of consciousness. Normally cerebral arterial blood flow is 50 mL/100 g brain/minute. When cerebral blood flow falls below 18 mL/100 g brain/minute, cerebral function falters but neurons may remain alive (Fig. 9.1). Thus, electrical activity ceases and sodium/potassium pumps begin to fail but the neurons are viable and can recover function if blood flow improves. In a stroke, this area of potential recovery is called an *ischemic penumbra*. Blood flow below 8 mL/100 g brain/minute results in neuronal death as early as 15 min after flow disruption. Neurons in the hippocampus and cerebellum are most sensitive to ischemia while neurons in the brainstem and spinal cord are the most resistant. Brain ischemia results in impaired energy metabolism with accumulation of calcium ions in the intracellular space, elevated lactate levels, acidosis, and production of free radicals. Cellular homeostasis is disrupted leading to neuronal death.

Stroke from occlusion of a specific cerebral artery causes a wedge-shaped infarction (Figs. 9.2 and 9.3). If a large artery occludes, such as the middle cerebral artery, the stroke may involve that entire vascular territory or portions may be spared depending on the degree of collateral circulation. In about 25% of ischemic strokes, there is rapid reperfusion of the ischemic territory from lysis of the embolic clot allowing blood to leak from damaged small arterioles, capillaries, and venules producing *hemorrhagic transformation* of varying degrees within the ischemic stroke.

Border zone or watershed infarctions are ischemic lesions that occur in characteristic locations at the junctions between two nonanastomosing arterial territories and constitute about 10% of ischemic infarctions. Hemodynamically, they usually develop from severe prolonged hypoperfusion of the watershed territory resulting from some combination of systemic hypotension, tight

Table 9.2 Risk factors for stroke

Risk factor	Increase in risk over normal age-matched population
Modifiable	
Hypertension	300–600 %
Diabetes mellitus	200–400 %
Smoking	150–300 %
Cocaine/Crack	200–500 %
Atrial fibrillation Untreated On warfarin	 300–500 % 50 %
Other heart abnormalities (mural thrombus, cardiomyopathy, acute myocardial infarction, mechanical heart valve, infective endocarditis)	200–600 %
Obesity	200 %
Serum lipid abnormalities	50 %
Asymptomatic carotid artery stenosis 60 to 74 % stenosis 75 to 94 % stenosis Greater than 95 % stenosis Total occlusion	(Five year increase) 10 % 14 % 10 % 5 %
Unmodifiable	
Advancing age	Relative rates double every decade after age 55 years
Male gender	25 %
Prior transient ischemic attack	400 %
Heredity (first degree relative with stroke)	100–400 % depending on cause

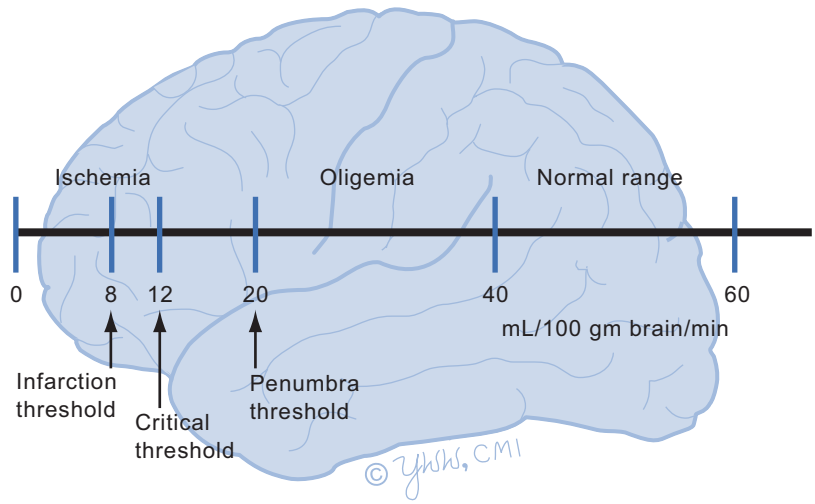

Fig. 9.1 Cerebral blood flow thresholds

stenosis or occlusion of extracranial or intracranial arteries, and microemboli that originate from the heart or the proximal stenotic artery lodging in distal intracranial arteries. The most common locations are between lenticulostriate and middle cerebral arteries and the middle and anterior cerebral arteries. The signs and symptoms produced are often mild, variable, and usually patients

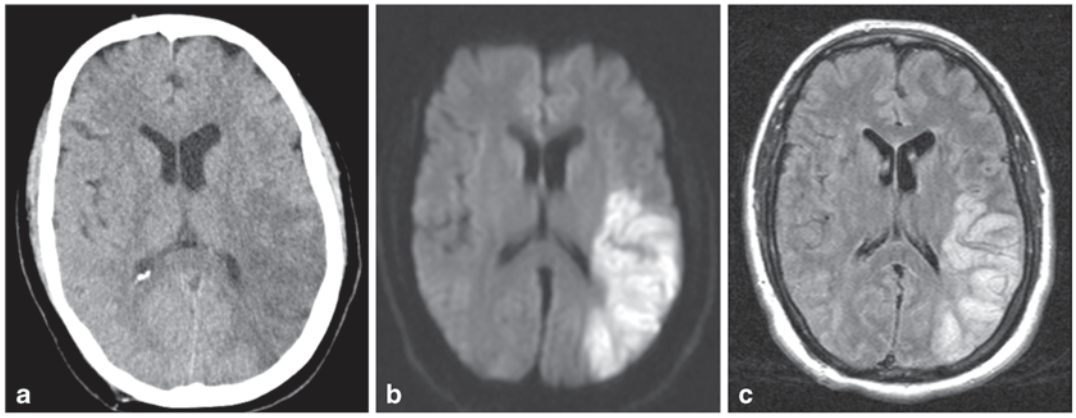

Fig. 9.2 Acute left middle cerebral artery wedge-shaped infarct shown by hypodensity on noncontrast head computed tomography (CT) (**a**), by bright signal on diffusion-weighted magnetic resonance imaging (MRI) (**b**) and by bright signal on T2 FLAIR MRI (**c**). (Courtesy of Blaine Hart, MD)

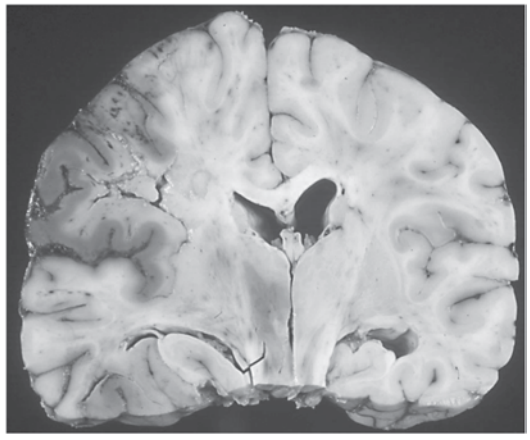

Fig. 9.3 Ischemic infarction, wedge-shaped pathologic specimen. (Courtesy of Mark Becher, MD)

make a good recovery. Exceptions are watershed brainstem infarctions involving branches of the basilar artery.

Microscopically, a large vessel ischemic stroke shows little visible changes until about 6 h later when swelling of neurons, astrocytes, and endothelial cells begins. Neurons first swell, then shrink, develop chromatolysis (nuclei become eccentric with hyperchromasia) and then die. Neutrophils are abundant after the first day. By second day microglia proliferate and become macrophages engulfing myelin breakdown products. Astrocytes proliferate, become reactive, and lay down glial fibers to produce gliosis. Neovascularity slowly develops and renourishes the damaged brain. Gradually over months the necrotic brain products are reabsorbed producing a glial lined cavity of variable size, seen on neuroimaging as encephalomalacia.

Lacunar ischemic strokes represent 25% of ischemic strokes and differ from large arterial strokes. They are small, less than 15 mm in diameter, and are primarily located in the basal ganglia, thalamus, brainstem, internal capsule, and centrum semiovale. Although many lacunes are silent producing with no symptoms, those that do cause clinical symptoms tend to be located at strategic sites where descending and ascending long tracts to and from the cortex are concentrated. Lacunes produce five well-recognized syndromes: pure motor hemiparesis (65%), sensorimotor stroke (20%), ataxic hemiparesis (9%), pure sensory stroke (5%), and dysarthria-clumsy-hand syndrome (1%). Acute lacunes are best recognized as small round lesions on magnetic resonance imaging (MRI) diffusion-weighted images. Older lacunes appear as hypointense small round cystic circles on T1-weighted MRI and must be distinguished from benign similar appearing vessels surrounded by a dilated Virchow–Robin space.

Lacunes are caused by arteriole microvascular occlusion of a single deep perforating artery less than 200 μ in diameter. The arterial pathology shows arteriolosclerotic or lipohyalinosis changes characterized by a disorganized occluded vessel wall, which has been replaced by connective tissue and surrounding macrophages. The predisposing factors for lacunes are unclear but advancing age and hypertension are the best recognized. The prognosis for good recovery is better than for major artery ischemic strokes. The rate of developing subsequent lacunes is 5% per year.

The mechanism of natural stroke recovery is incompletely understood. Possible mechanisms for motor recovery include: early recovery of motor neuronal excitability as blood flow increases; and later, (1) activation of partially spared corticospinal tract pathways; (2) alternate behavioral strategies to use limbs; (3) expansion or neuroplasticity of functional motor cortex within its existing normal domain; and (4) neuroplasticity of motor cortex within a new brain area. There is increasing evidence that the motor cortex is not fixed but plastic and can expand or shrink within the existing site based on clinical demand and can even move motor function to remote sites. However, movement of the motor cortex to a different gyrus likely occurs only in young children.

Major Clinical Features

Onset is sudden or the patient awakens from sleep with the completed stroke but rarely the stroke signs can progress over 1–2 days. Table 9.3 lists the common clinical features of lacunar, anterior circulation, and posterior circulation strokes while Fig. 9.4a, b show the location and distribution of the major arteries. Most cortical strokes are symptomatic but only one-third of lacunes are symptomatic. Overall in cortical ischemic strokes, the hemiparesis is severe in 60%, moderate in 20%, and mild in 20%. Broca's aphasia is more common than Wernicke's aphasia but in large left middle cerebral artery strokes, a global aphasia will be present (see Chap. 11 on disorders of higher cognitive function).

Major Laboratory Findings

Tests are performed to diagnose a stroke, identify its location and determine the cause and source. Computed tomography (CT) scans are excellent to detect a hemorrhagic stroke but often appear normal for 6 to 24 h following an acute ischemic stroke. Subtle effacement (loss of boundaries) of sulci is the earliest sign followed by development of a hypodense region due to development of cytotoxic and vasogenic edema. In general, the larger the stroke the earlier it becomes visible on neuroimaging. MRI is the most sensitive neuroimaging method to detect an ischemic stroke. While conventional MRI may appear normal for several hours, diffusion-weighted MRI will show an area of hyperintensity in the territory of the infarct within 4 h. Diffusion-weighted MRI scans are helpful to distinguish an acute stroke from older strokes that are not hyperintense. Within 8 h, edema from the infarction appears hyperintense on T2-weighted images and hypointense on T1-weighted images. MRI is sensitive for small lacunes and infarctions in the brainstem and cerebellum that may be missed by CT. In a patient with a lacunar stroke it is common to identify other older lacunes that were clinically silent.

Several tests are used to determine the cause of the stroke. Imaging of the extra- and intracranial vessels is done with either magnetic resonance angiography (MRA) or CT angiography (CTA) and can identify medium to large diameter stenotic or occluded arteries in the neck and head. Extracranial Doppler ultrasonography examination of the carotid artery in the neck also detects narrow or occluded vessels. Transthoracic or transesophageal echocardiogram can detect clots or masses within the heart, vegetations on heart valves, immobile cardiac wall segments, and cardiomegaly that point to a cardioembolic source. Cerebrospinal fluid (CSF) examination is seldom necessary but abnormal CSF can indicate a vasculitis or meningitis and CSF culture may determine the cause of the meningitis. A variety of blood tests can look for a coagulopathy or vasculopathy (see transient ischemia attack section for details).

Table 9.3 Clinical features of common strokes

Arterial territory of stroke	Clinical presentation[a]
Left middle cerebral artery (mid frontal and parietal lobes)	Aphasia, contralateral hemiparesis, contralateral hemisensory loss, homonymous hemianopia, dysphagia
Right middle cerebral artery (mid frontal and parietal lobe)	Contralateral hemiparesis, contralateral hemisensory loss, homonymous hemianopia, dysphagia, apraxia
Anterior cerebral artery (frontal pole and medial aspect of frontal and parietal lobes)	Contralateral leg weakness and sensory loss
Vertebral/basilar artery	
Wallenberg's syndrome from posterior inferior cerebellar artery (medulla and cerebellum)	Vertigo, nystagmus, dysphagia and dysarthria with ipsilateral Horner's (miosis, ptosis, and diminished sweating on face) diminished facial pain and temperature perception, limb ataxia and contralateral loss of trunk and limb pain and temperature
Mid basilar artery (pons and cerebellum)	Often involves bilateral branches producing signs that include facial weakness, quadraparesis, dysarthria, dysphagia, vertical and horizontal nystagmus, ptosis, skew deviation of vision, limb ataxia, and diminished level of consciousness Locked-in syndrome occasionally develops with complete loss of voluntary limb and face movement, retained consciousness and voluntary vertical eye movements
Top of basilar artery (midbrain, occipital lobes and temporal lobes)	Involves midbrain and posterior cerebral arteries producing disruption of voluntary vertical gaze, third nerve palsies, ataxia, somnolence, homonymous hemianopia or quadrantopia, and occasionally loss of recent memory
Lacunar stroke territory	
Internal capsule	Contralateral hemiparesis, hemisensory loss without aphasia or visual loss
Upper half brainstem/cerebellum	Combinations of ataxia, vertigo, diplopia, dysarthria, Horner's sign, contralateral sensory loss, ipsilateral facial weakness, ipsilateral facial sensory loss
Lower half brainstem	Contralateral hemiparesis without sensory loss (pure motor stroke)

[a] Clinical features may be less than described due to the arterial occlusion being only a branch and not the entire artery or there is good collateral circulation minimizing the size of the infarction

Principles of Management and Prognosis

Treatment goals of the acute ischemic stroke are to (1) minimize the size of the stroke, (2) maximize the extent of functional recovery, and (3) minimize the risk of subsequent strokes.

Patients with moderate to severe strokes require immediate hospitalization and monitoring, often in an intensive care unit. Myocardial injury associated with an acute stroke develops in 15% and occasionally leads to systemic hypotension, serious cardiac arrhythmias such as atrial fibrillation, and ventricular myocardial wall motion abnormalities with subsequent creation and discharge of new cardiac emboli. However, minor changes in the electrocardiogram (EKG) are common and often called "reversible stunned myocardium," presumably due to sympathetic relative hyperactivity and catecholamine release caused by the stroke.

Management of hypertension is controversial but the blood pressure should be lowered if the initial systolic blood pressure is very high (systolic >220 mm Hg or diastolic >105 mm Hg) or (>185 mm Hg/110 mm Hg if thrombolytics were given). In general, blood pressures up to 185 mm Hg systolic are not lowered by antihypertensives as studies demonstrated lowering moderate hypertension did not benefit outcome measures. Severe hypotension is detrimental as it lowers the cerebral perfusion pressure and should be corrected. Pulmonary complications including low pulse oximetry, secondary pneumonias, and pulmonary emboli develop in 20% during the

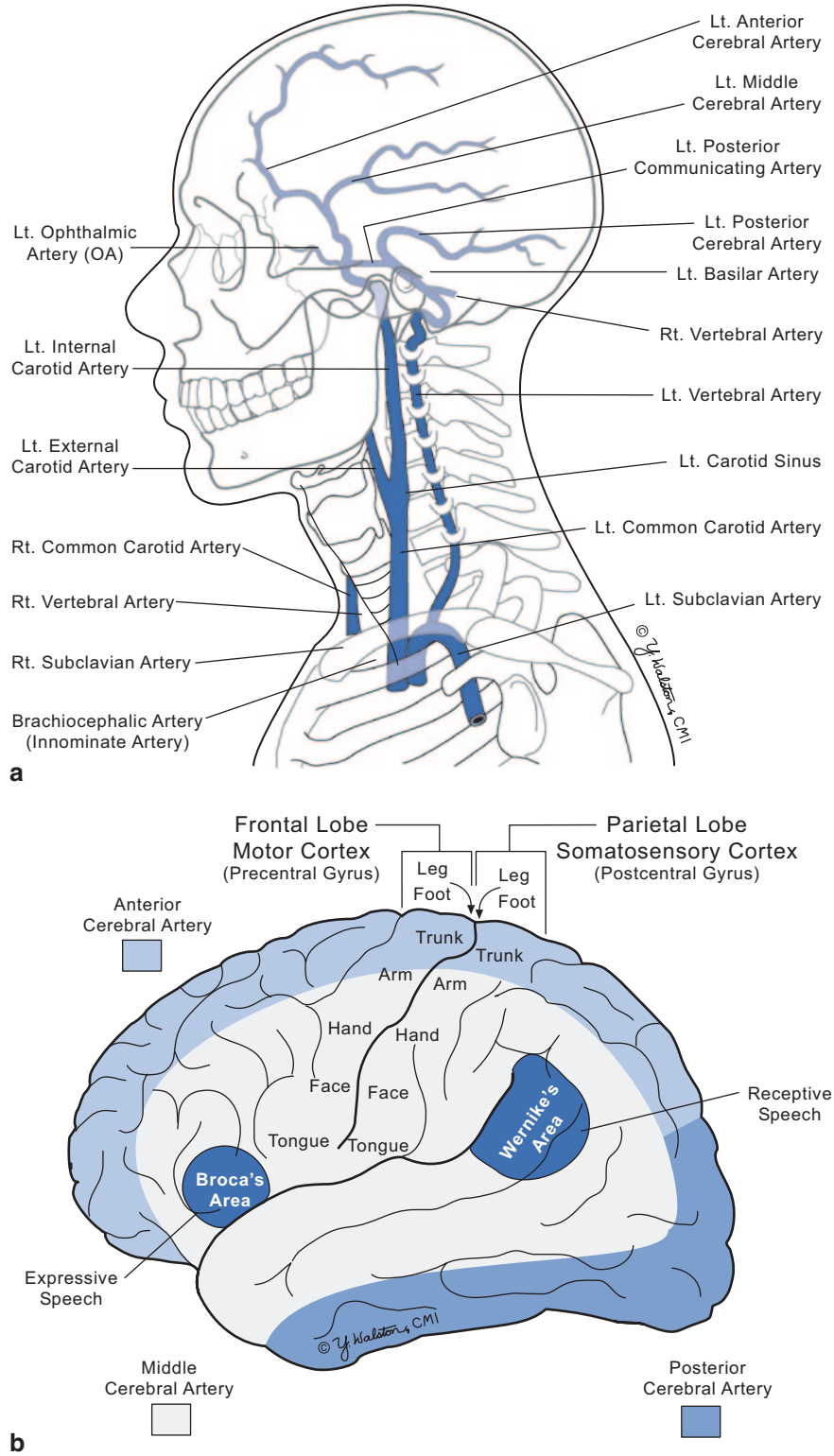

Fig. 9.4 Arterial supply of the brain. **a** Major vessels **b** Vascular territories

first week after a stroke and should be treated. Fever at the time of the acute stroke has a worse outcome but lowering the body temperature safely is difficult and currently not recommended. Patients with hyperglycemia at the time of the acute stroke are recognized to have poorer outcomes than normoglycemic patients, but studies to date have not demonstrated clear benefit from lowering the blood glucose with insulin.

Intravenous recombinant tissue plasminogen activator (rt-PA) alteplase is beneficial if given within 4.5 h of onset of the acute ischemic stroke in selected patients. The earlier the intravenous rt-PA is administered, the greater the benefit. The benefits are in reducing long-term disability and being independent when evaluated at 3 months (but not immediately after rt-PA administration). The major risk factors for rt-PA administration are diagnosis error, large size stroke, hypertension, hyperglycemia, and age above 80 years. To receive rt-PA, patients must meet strict entry criteria including (1) absence of blood on a CT scan, (2) presence of a small to moderate sized stroke, (3) no history of recent myocardial infarction, gastrointestinal bleeding, surgery, or anticoagulation, (4) no bleeding abnormality or elevated prothrombin time by an elevated *international normalized ratio* (INR) usually from taking warfarin, and (5) reliable onset of stroke symptoms within 4.5 h of rt-PA dose. Even if the criteria are met, rt-PA administration carries a 6.5% risk of hemorrhagic transformation of the stroke that occasionally can worsen outcome. When following the above criteria, only about 10% of patients with acute ischemic strokes meet the eligibility criteria and are administered rt-PA.

Patients should begin rehabilitation as soon as they are physically and mentally able to participate. Patients with Broca's aphasia benefit from speech therapy first to improve communication by gesturing and later by speaking. Patients with motor weakness require training in transferring, dressing, standing, and eventually walking. Since 20% of patients develop venous thrombosis in the paretic leg, subcutaneous heparin should be administered until the patient begins ambulating. Most major strokes cause dysphagia of both liquids and solids. Frequently a nasogastric feeding tube or gastrostomy is needed to maintain adequate nutrition until spontaneous recovery of swallowing occurs up to 2 months later. Patients lacking a good cough reflex are at a risk for aspiration pneumonia.

Natural recovery from most strokes occurs over 3–6 months. In general 70% of motor recovery occurs in the first month and 90% occurs by 3 months. Recovery of speech is slower with 90% recovery by 6 months. In hemiparetic patients, 80% walk again, but only 10% regain full use of the paretic hand. Factors associated with a good recovery include young age, mild stroke severity, high level of consciousness, previous independence, living with a partner, high frequency of social contacts, and positive mood. The latter factors suggest that patient motivation is important in recovery. Prevention of subsequent strokes is covered in the subsection on transient ischemic attacks.

Transient Ischemic Attack

Introduction

A transient ischemic attack (TIA) has a new definition: *A brief episode of neurologic dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting less than 1 h and without evidence of acute infarction*. This definition replaces the old one: The sudden onset of monocular visual loss or focal neurologic symptoms that stem from one vascular territory and completely clear within 24 h. The new definition recognizes that most TIAs last around 20 min and clinical symptoms are rapidly cleared but the MRI may still demonstrate that the patient actually experienced a small ischemic stroke.

The incidence of TIAs varies between studies and is complicated by many patients failing to report a TIA to their physician or that when a patient does see a physician, the TIA is over and the physician must rely on the patient's history. When actual TIAs were evaluated by physicians during the episode, only two-thirds were actually diagnosed as a TIA with the others being diagnosed as migraine auras, trauma, seizures,

and psychological events such as an acute anxiety or panic attack. A reasonable estimate is that 250,000 TIAs annually occur in the USA.

The significance of a TIA lies not in the event but that a TIA portends a future stroke. The 90 day risk of stroke after a TIA has been reported as high as 17%. Studies report that one-third of patients who develop a subsequent stroke do so within the next 2–7 days. A TIA also elevates the risk of acute cardiac disease (myocardial infarction, unstable angina, or ventricular arrhythmia) in the next few months.

Several risk factors are independently associated with a stroke following the TIA: age over 60 years, hypertension, elevated serum cholesterol, atrial fibrillation, high-grade carotid stenosis, diabetes mellitus, smoking, neurologic signs lasting longer than 1 h, heavy alcohol use; and obesity (Table 9.2). Many risk factors can be rapidly modified so that a prompt evaluation for these factors is needed.

Pathophysiology

Although incompletely understood, a TIA likely results from brief occlusion of a cerebral or central retinal artery by a platelet embolus that lodges in the artery and then rapidly breaks up or by a transient event that alters circulation dynamics and perfusion through a tightly stenotic artery. By definition, diffusion-weighted MRI scans are normal and no evidence of an infarction is found at autopsy.

Major Clinical Features

TIAs symptomatically fall into three large arterial territories; (1) ophthalmic artery, (2) branches of internal carotid cerebral arteries, or (3) vertebrobasilar artery. Transient monocular blindness or *amaurosis fugax* results from transient occlusion of the ophthalmic artery. This produces a painless, brief (minutes) sudden loss of sight involving all or part of the visual field of one eye. The visual loss is commonly described as a curtain drawn upward or downward over one eye that persists for minutes and then the curtain slowly reversing itself to restore vision. Permanent loss of vision is rare. Fundoscopic examination of retina is usually normal, although, occasionally tiny cholesterol emboli from a carotid artery plaque may be seen. Patients should not have bilateral visual loss or see lights flickering in the eye when it is closed. The latter suggests a migraine aura or retinal tear.

TIAs involving the middle cerebral artery are the most common presentation because that artery has the highest blood flow. Patients commonly present with sudden, painless onset of contralateral limb weakness (hemiparesis or monoparesis), and partial loss of touch and temperature sensation in the involved limbs. If the middle cerebral artery in the dominant hemisphere is affected, patients often develop an expressive or occasionally global aphasia.

TIAs involving the vertebrobasilar system most commonly produce a combination of hemiparesis, vertigo, ataxia, diplopia, dysarthria, and blurred vision in both eyes but rarely cause isolated vertigo or loss of consciousness.

Workup of a patient with a TIA to establish the cause should be performed as rapidly as possible due to the increased risk of future stroke.

Major Laboratory Findings

An MRI with diffusion-weighted imaging can rule out an acute ischemic or hemorrhagic infarction or other mimics of TIA. The most common important arterial lesion is stenosis (70–99%) of the internal carotid artery at the bifurcation from the common carotid artery on the side contralateral to the patient's symptoms. Dissection of the carotid arterial wall occasionally may be identified. The presence of atrial fibrillation or cardiomyopathy also carries a high risk for subsequent stroke. However, for many TIAs the cause is not found.

Principles of Management and Prognosis

Immediate management is to evaluate the patient for modifiable risk factors and improve them. The highest risk factors for subsequent stroke are the presence of cardiac thrombi, atrial fibrillation, or marked stenosis of the internal carotid artery. Thus immediate workup commonly involves an EKG looking for a myocardial infarction or atrial fibrillation. If there is a prior history of heart disease, a transthoracic echocardiogram looking for mural thrombi in the heart or valves or low ejection fraction of 20% or less is useful. There are several methods to evaluate the carotid artery for high-grade stenosis that include carotid duplex (current gold standard), magnetic resonance angiogram (MRA) of the head and neck, computed tomography angiogram (CTA) of the head and neck, and cerebral arteriogram. A stenosis of 70–99% identified on the symptomatic carotid artery should be considered for an elective and fairly rapid (within 2 weeks) carotid endarterectomy. In general, an elective surgical endarterectomy reduces the risk of a stroke over the next 5 years by 7%. However, there is an immediate risk of surgical complications that ranges from 3 to 6% even when performed by an experienced surgeon. Studies have shown that after the endarterectomy, failure to reduce modifiable stroke risk factors in the patient offers limited long-term benefit and a high rate of stenosis recurrence. In some patients, endovascular surgical placement of a carotid stent is being done but current outcome results are not superior to endarterectomy.

Reducing the blood pressure in patients with hypertension (systolic BP > 140 mm Hg or diastolic BP > 90 mm Hg) reduces the stroke risk by 30–40%. A number of other risk factors presented in Table 9.2 if found should be treated to lower risk of subsequent stroke. Lowering elevated blood, low-density lipoprotein cholesterol (LDL-C > 100 mg/dL) levels should be done. Patients should be encouraged to bring their weight down to the ideal level and to stop smoking. Evaluation for hypercoagulable state can be done by a series of blood tests in younger patients with stroke in whom no clear cause has been identified. Commonly ordered tests include screening for lupus anticoagulant, anticardiolipin antibodies, deficiency of proteins C and S, and antithrombin III and hemoglobin SS in African American patients. If atrial fibrillation is identified, patients should be considered for warfarin or the newer oral anticoagulant medications as these medications reduce the stroke risk by 40%.

Medical treatment for most patients involves administration of platelet aggregation inhibitors beginning with daily aspirin and advancing to clopidogrel or dipyridamole if the patient does not tolerate aspirin or continues to have TIAs. Use of daily low dose (80 mg) aspirin has been shown to reduce the risk of stroke by 20% in high-risk patients and 5% in the general population. Patients taking daily aspirin should not take Nonsteroidal antiinflammatory drugs (NSAIDs) more than twice a week as they interfere with the benefit of the aspirin.

Hemorrhagic Strokes

Overview

Intracranial hemorrhages occur in three intracranial spaces: intraparenchymal/ventricular, subarachnoid, and subdural/epidural. Subdural hematomas are discussed in the Chap. 18 on traumatic brain injury. The significance of blood in the subarachnoid space is not that it causes immediate clinical symptoms (headache, stiff neck, etc.) but that it often comes from a ruptured aneurysm that causes life-threatening parenchymal damage.

Spontaneous Intracerebral Hemorrhage

Introduction

Nontraumatic intracerebral hemorrhage (ICH) is bleeding into the brain parenchyma that may extend into the ventricles and rarely into the subarachnoid space. In the USA each year an estimated 45,000 people experience an ICH with an annual incidence of 15–20 cases per 100,000

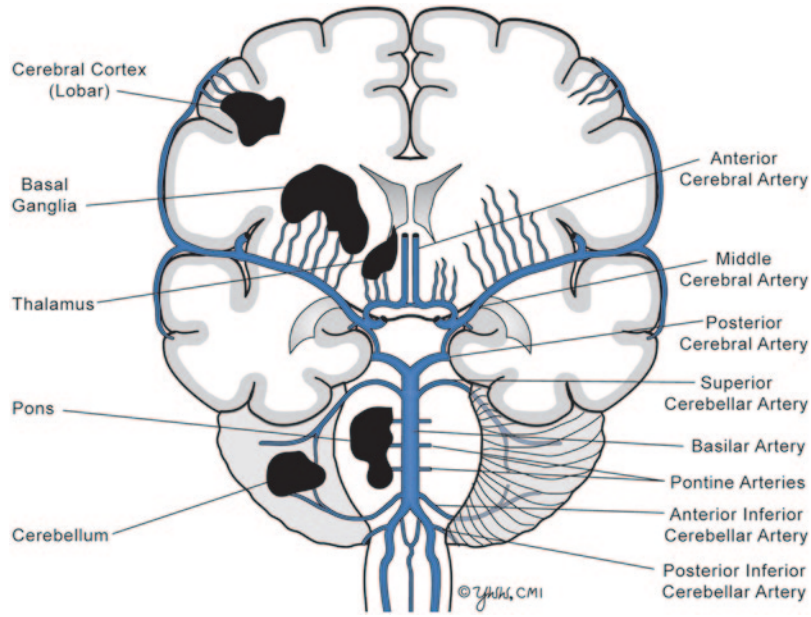

Fig. 9.5 Common sites of intracerebral hemorrhages

people. ICH is more common in men, African Americans and Japanese. Spontaneous intracerebral hemorrhages account for only 10% of all strokes but have the highest mortality rate.

Primary ICH represents 85% of cases. About 80% develop from spontaneous rupture of small arteries associated with hypertension and 20% from amyloid angiopathy. Secondary intracerebral hemorrhages occur from arteriovenous malformations, usage of sympathomimetic drugs such as methamphetamine, bleeding tumors, or impaired anticoagulation. Long-term anticoagulation results in a tenfold increase in risk of ICH and is becoming more common since anticoagulation is increasingly used in patients with atrial fibrillation.

Pathophysiology

Intracerebral hemorrhages (hematomas) most commonly occur in the cerebral lobes, basal ganglia, thalamus, pons and cerebellum (Fig. 9.3). The bleeding usually results from rupture of penetrating arteries originating from the basilar artery or the anterior, middle, or posterior cerebral artery. About 50% of ICH arise in the basal ganglia from lenticulostriate arteries and 10% occur in the thalamus (Fig. 9.5). However, smaller and subtle cerebral microbleeds resulting from leaky cortical and perforating vessels are being increasingly detected by MRI. Currently the cause of this vasculopathy is unclear.

The exact means by which ICH occurs is poorly understood but hypertension induces arteriosclerosis that results in fibroblast proliferation and deposition of lipids within the subintima of the artery. Involved arteries become both narrow and stiff as there is replacement of smooth muscle cells with collagen. These arteries then can either occlude causing infarction or tear causing a focal hemorrhage. In 10% of ICH small microaneurysms are found but for most patients no bleeding source is indentified.

Following vessel rupture, blood under arterial pressure rapidly flows into adjacent brain and often into ventricles. Intraventricular hemorrhage develops in almost half of patients with ICH. When blood enters ventricles, particularly the third ventricle, abrupt deterioration in consciousness develops. Clot formation often occurs which can lead to obstructive hydrocephalus and its consequences.

The cerebral bleeding often stops by tamponade within 30 min but CT studies show that 40% have expansion from the initial hemorrhage size.

In hemorrhages that expand, 75% have hematoma expansion within the first 6 h while the rest show expansion within the first 24 h. There is some evidence that slow bleeding from the ruptured vessel can continue for hours. The route of hematoma expansion is often along white matter tissue planes.

Red blood cell lysis occurs 6–8 days after the hemorrhage and is mediated by complement-activated membrane attack complexes. Release of hemoglobin and its byproducts are believed to be involved in neural toxicity. Macrophages invade the clot and phagocytose red blood cells and remove blood products over several months.

The surrounding compressed brain develops vasogenic edema from release and accumulation of osmotically active clot proteins and cytotoxic edema from compression of surrounding blood vessels producing secondary tissue ischemia. The edema begins in the first day, peaks in 5–7 days and persists for up to 2 weeks. Large areas of edema correlate with a poor outcome. Months later there is only a small cavity at the site of the original hemorrhage whose orange-stained walls contain hemosiderin-laden macrophages.

Cerebral amyloid angiopathy (CAA) is the second most common cause of ICH and develops mainly in adults over age 70 years. CAA affects primarily leptomeningeal and cortical vessels of neocortical regions, especially in the occipital cortex. CAA is uncommon in the thalamus, basal ganglia, and white matter, locations where hypertensive ICH commonly occurs. CAA is unrelated to a systemic disease but occurs from deposition of β-amyloid protein into the tunica media and adventitia of cortical arterioles and small arteries causing the vessel walls to initially thicken and then become thin from splitting of the arteriole walls. Some vessels develop fibrinoid necrosis and microaneurysms that are associated with hemorrhages. Vessels infiltrated with CAA can be histopathologically best seen with Congo-red, Thioflavin S, or anti-Aβ antibody stains.

As CAA vessels become more fragile, cortical lobar hemorrhages and microhemorrhages develop. In addition, amyloid deposition of vessels may initially thicken the walls predisposing to occlusions and microinfarctions that are commonly present. The source of the β-amyloid is unclear for CAA and the association with the amyloid plaques of Alzheimer's disease is uncertain and does not hold true for all patients.

Major Clinical Features

The most common hemorrhage locations are the putamen, thalamus, and caudate (60% of total). These patients may suddenly become aware of "something wrong" followed minutes later by progressive depression of consciousness, vomiting, headache, contralateral hemiparesis, and abnormal eye movements. Signs of a cerebral hemorrhage depend upon the lobe involved. When the hemorrhage invades the ventricles, patients rapidly developed a depressed level of consciousness. A cerebellar hemorrhage usually begins in the dentate nucleus with blood expansion into one cerebellar hemisphere producing headache, ipsilateral limb ataxia, vertigo, and vomiting without limb weakness. Patients with amyloid angiopathy often experience a lobar hemorrhage with signs depending on the lobe involved.

Major Laboratory Findings

The CT scan establishes the diagnosis by the presence of an acute ICH (Figs. 9.6 and 9.7). Secondary findings include surrounding cerebral edema, intraventricular hemorrhage, and findings of brain herniation (see Chap. 18 on traumatic brain injury and subdural hematoma for details). In 40%, repeat CT scans show expansion of the hematoma in the first 24 h. Cerebral angiography is occasionally needed to diagnose less common causes of ICH such as aneurysms, arteriovenous malformations, dural venous thromboses, and vasculitis.

Principles of Management and Prognosis

The goals of management are to improve survival from the acute hemorrhage, to identify the

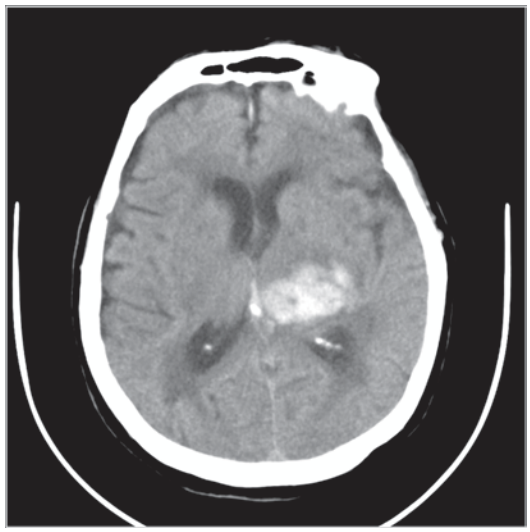

Fig. 9.6 Computed tomography (*CT*) scan of acute intracerebral hemorrhage in left thalamus due to hypertension. (Courtesy of Blaine Hart, MD)

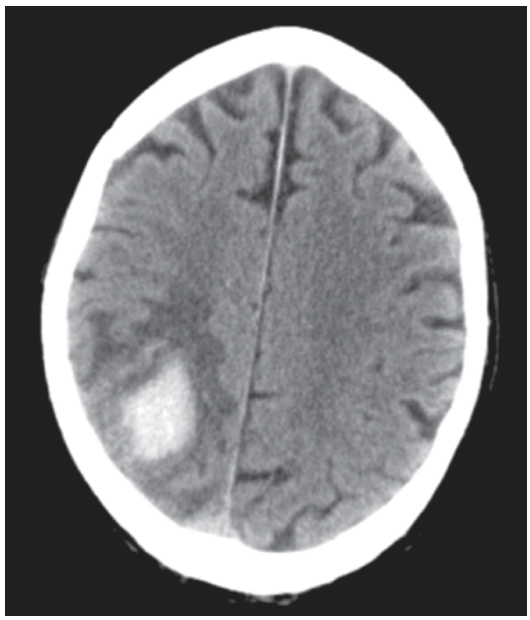

Fig. 9.7 Computed tomography (*CT*) scan of acute lobar intracerebral hemorrhage in right fronto-parietal lobe with surrounding vasogenic edema due to amyloid angiopathy in an 80-year old man. (Courtesy of Blaine Hart, MD)

etiology, and to prevent future bleeds. The acute management of an ICH is particularly challenging as the hemorrhage may cause transtentorial herniation. Patients often require early intubation and placement on a ventilator to control the airway, insure sufficient oxygenation, and to prevent tracheal aspiration. Frequent monitoring of vital signs and cardiac status are needed as patients often deteriorate in the first 24 h. Cardiac arrhythmias may develop that required treatment. Patients commonly have an elevated blood pressure when hospitalized. However, the optimal level of blood pressure is uncertain but very elevated systolic blood pressures above 220 mm Hg are usually reduced to less than 160/90 mm Hg. Hypotension always should be immediately corrected as it lowers intracerebral perfusion pressure.

Intravenous administration of recombinant factor VII (rFVIIa) has been tried to improve homeostasis and minimize hematoma expansion but is only considered in the setting of coagulopathy. Management of impending brain herniation is difficult. Mannitol or hypertonic saline is often tried but has not been very successful and corticosteroid administration is considered detrimental. Seizures develop in 15% during the first few weeks after hemorrhage. Patients require anticonvulsants as a generalized seizure raises intracranial pressure, which could increase the risk of brain herniation. However, prophylactic anticonvulsants are not currently recommended.

If the patient develops signs of brain herniation, repeat CT scans can determine if hematoma expansion or intraventricular hemorrhage occurred or there is obstructive hydrocephalus. Attempts to surgically remove the blood clot are controversial as limited evidence exists that surgery improves quality or duration of survival. However, a moderate to large (>3 cm) cerebellar hematoma is an exception and is a surgical emergency as removal of the hematoma carries a significant improvement in mortality and morbidity. Placement of a ventriculostomy or intraventricular shunt if hydrocephalus develops to remove ventricular blood does reduce intracranial pressure. Ventricular administration of rt-PA may be given to help break up ventricular clots that often block the shunt tubing.

Patients who survive the acute phase should be evaluated for the etiology of the bleed. This may require a cerebral arteriogram to diagnose an aneurysm or arteriovenous malformation and

MRI with gadolinium to identify a hemorrhagic tumor. Surgical removal of an arteriovenous malformation may be indicated if identified. Currently there is no easy method to diagnose cerebral amyloid angiopathy.

Rehabilitation of surviving patients aims at improving limb strength, gait, and speech. Control of the hypertension is essential. However, patients with a hypertensive hemorrhage seldom experience a second hemorrhage. Prevention of rebleeding in patients with amyloid angiopathy is presently impossible and patients have a recurrence rate of 10% per year. Rebleeding from arteriovenous malformations can occur at up to 18% chance per year.

Unfortunately, in over 25% of patients the mass from the blood clot and surrounding cerebral edema produces immensely increased intracranial pressure leading to secondary brain herniation and death within hours to a few days. The overall 1-year survival rate from an ICH is 35% but only 20% of survivors are independent at 6 months. In small hemorrhages, however, neurologic sequelae may be less severe compared to a similar sized ischemic stroke because neuronal tissue was compressed by the hemorrhage and therefore less destroyed.

Saccular Aneurysms and Subarachnoid Hemorrhage (SAH)

Introduction

SAH is the presence of blood in the meninges and CSF. Head trauma, the leading cause of SAH, is discussed in Chap. 18 on traumatic brain injury and subdural hematoma. Excluding trauma, the annual incidence of spontaneous SAH is 10 cases per 100,000 and accounts for 3% of all strokes. Aneurysm SAH is uncommon in infants and children, has a mean age of onset in the sixth decade and is less common in the elderly. Thus, the average patient with aneurysmal SAH is considerably younger than the patient with an ischemic stroke. Women outnumber men with a ratio of 3:2, and African Americans outnumber Caucasians with a ratio of 2:1.

At least 85% of SAH is due to rupture of a saccular (berry) or fusiform aneurysm and account for 30,000 individuals per year in the USA. Saccular aneurysms are outpouchings of midsized cerebral blood vessels while fusiform aneurysm are dilated elongated segments of the vessel. Saccular aneurysms rupture much more often than fusiform aneurysms. The remaining causes of aneurysms include vasculitis, superficial arteriovenous malformations of the brain and spinal cord, and mycotic aneurysms due to septic emboli that weaken the wall of the occluded arteriole.

Major risk factors for rupture of an aneurysm include hypertension, smoking, heavy alcohol consumption, cocaine, and a positive family history. Five percent of patients with SAH have a positive family history and first-degree relatives have a fivefold risk of SAH.

Pathophysiology

Autopsy studies estimate the prevalence of unruptured saccular aneurysms at 2%—with 30% of these patients having multiple aneurysms. The location of saccular aneurysms is mainly at the bifurcation of larger vessels or at sites where disturbances of blood flow are generated (Fig. 9.8). About 90% of aneurysms develop in anterior cerebral arteries that are branches of anterior part of the circle of Willis and 10% from posterior cerebral arteries that are branches of the vertebral arteries. The most common aneurysm locations are anterior communicating artery (40%), posterior communicating artery (20%), and bifurcation of the middle cerebral artery (15%). Except for a few hereditary diseases, patients with cerebral aneurysms do not have systemic aneurysms.

The pathophysiology by which saccular aneurysms develop is incompletely understood. Current evidence suggests the aneurysm is not congenital but develops into a mature aneurysm in adulthood since children seldom experience a ruptured aneurysm and autopsy studies of infants and children rarely find aneurysms. The origin of the aneurysm is just distal to a bifurcation where wall shear forces are high. The aneurysm wall is

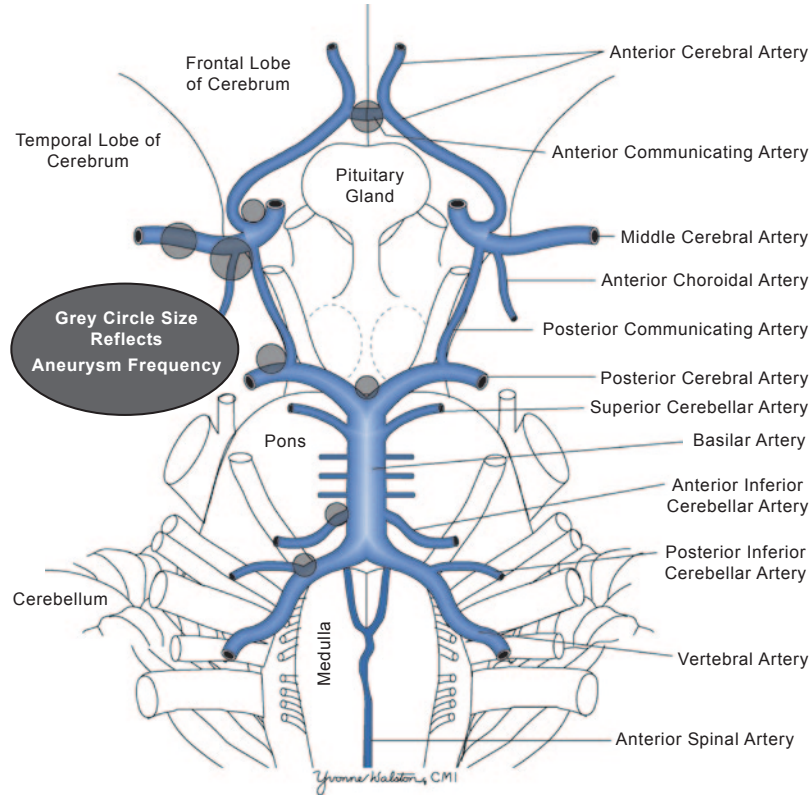

Fig. 9.8 Distribution of saccular aneurysms

characterized by reduction of collagenous fibers, atrophy of tunica media, and loss of internal elastic lamina in addition to the expected absence of external elastic lamina. The histologic appearance of the artery wall before and after the aneurysm is normal. The role of genetic factors in the pathogenesis is unclear.

The risk of bleeding from an aneurysm increases considerably by the size of the aneurysm. In general, the annual risk of rupture of a previously unruptured berry aneurysm is <0.5% for those less than 7–10 mm diameter, 1–3% for 10–24 mm diameter, and 8% for those larger than 24 mm. Patients with multiple aneurysms also are at higher risk of rupture.

Vasospasm often develops in arteries that are surrounded by collections of clotted subarachnoid blood producing narrowing of the lumen secondary to direct effect of blood on the adventitia. The distal cerebral ischemia territory may become infarcted if there is lack of sufficient blood supply from the parent artery and insufficient collateral blood flow. Arteries in chronic vasospasm can develop necrotic smooth muscle in the media with neutrophils infiltrating the adventitia.

Major Clinical Features

At the rupture of an aneurysm, arterial blood under high pressure flows in the subarachnoid space. The aneurysm rupture usually occurs when the patient is awake and not sleeping. The patient usually develops a sudden explosive headache, the cardinal feature, within seconds of a rupture. Patients may rapidly become unconscious but usually present to the emergency room with a severe headache, stiff neck, relative preservation of consciousness, and few or no localizing neurologic signs. However, in patients presenting to an emergency room with a severe sudden onset headache, less than 10% prove to have a SAH with the other 90% due to a migraine headache or meningitis. Vomiting is a presenting symptom

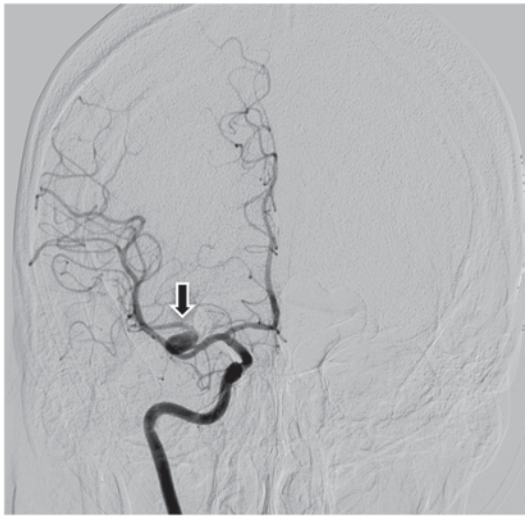

Fig. 9.9 : Cerebral angiogram of right carotid showing right middle cerebral artery saccular aneurysm (*arrow*). (Courtesy of Blaine Hart, MD)

in 70% of patients. Since the blood is in the subarachnoid space, the patient initially may have no focal neurologic signs or develop cranial nerve palsies including dilated pupils, disconjugate gaze, facial weakness, dysphagia, and dysarthria. Seizures occur in 10% of patients. Subhyloid intraocular hemorrhages develop in 15%. These hemorrhages are caused by a sustained increase in CSF pressure, with obstruction of the central retinal vein as it traverses the optic nerve sheath. Linear streaks of blood called flame-shaped hemorrhages appear in the preretinal or subhyloid layer usually near the optic disk.

Vasospasm commonly develops 5 to 15 days later producing a variety of focal neurologic signs that include hemiparesis, aphasia, and other neurologic signs depending on the artery in spasm. These signs develop from severe ischemia in the involved cerebral territory that may lead to infarctions.

Severe obstructive hydrocephalus often follows a SAH in about 15% from obstruction of cerebral CSF pathways and may require CSF shunting if it does not spontaneously subside. Occasional giant and fusiform aneurysms produce neurologic deficits by mass effect and may cause a third nerve palsy or other cranial nerve deficits (Fig. 9.9).

Major Laboratory Findings

The diagnosis of SAH is best made by CT, which is widely available, rapidly performed even in a restless patient, and identifies blood in the subarachnoid space over 90% of the time. The characteristic hyperdense appearance of extravasated blood in the basal cisterns is the most common finding (Fig. 9.10). Collections of extravasated blood elsewhere may suggest the site of the bleeding aneurysm. In 30% of patients, there is also an intraparenchymal hematoma due to rupture of the aneurysm directly into the brain.

CT best detects bloody CSF when there is a RBC concentration of greater than 0.5%. A lumbar puncture will detect fresh blood in the CSF as early as 1/2 h after the bleed and the early cell count shows the same number of RBCs in every tube. Centrifugation of the blood and comparison of supernatant color with water against a white background is similar. The CSF pressure is usually elevated. A lumbar puncture (LP) done after 8 h should show xanthochromia (yellow color) of the CSF supernatant establishing the diagnosis of SAH.

Several methods exist to identify the location of the aneurysm and whether other aneurysms coexist. The gold standard is four-vessel catheter angiography as it gives the best view of the aneurysm shape. However, an angiogram is time consuming, difficult to perform on a sick patient, and carries a complication rate of rebleeding in 2–5%. CTA using contrast media is becoming popular because it is faster, safer, and has a sensitivity of 95% for aneurysm greater than 4 mm. Because MR angiography is slower, technique dependent, and difficult to perform in a patient on a ventilator, it is less helpful.

Principles of Management and Prognosis

The goal is to maximize the quality of survival from the acute SAH, minimize the vasospasm, and to eliminate the aneurysm, thus preventing rebleeding.

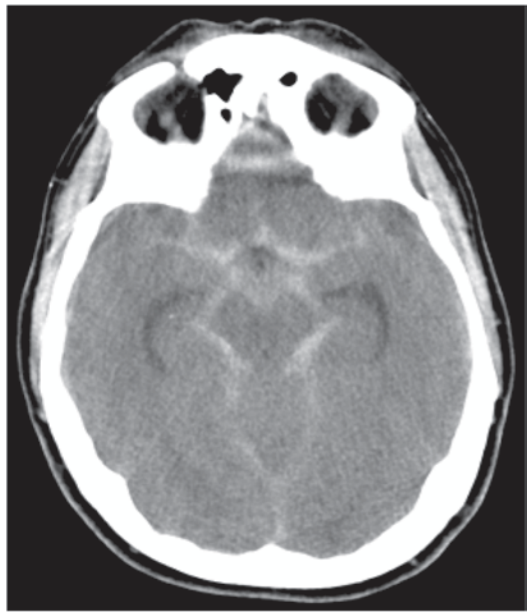

Fig. 9.10 Computed tomography (CT) scan of subarachnoid hemorrhage. (Courtesy of Blaine Hart, MD)

Table 9.4 General grading systems for ruptured saccular aneurysms. (Includes Hunt Hess and Botterell and Lougheed scales)

Grade	Clinical characteristics
1	Alert, minimal headache, slight neck stiffness and no neurologic deficit
2	Alert, moderate-severe headache, stiff neck, and no neurologic deficit other than cranial nerve palsy
3	Drowsiness, mild confusion with mild neurologic deficit
4	Semicoma, moderate-severe hemiparesis, possible early decerebrate rigidity
5	Deep coma, decerebrate rigidity, moribund

Patients are often classified as to severity and prognosis based on the Glasgow coma scale and other scales (Table 9.4). Patients should be placed in an intensive care unit as they often deteriorate during the first day. If mental status and breathing deteriorates, intubation and mechanical ventilation is required. The blood pressure should be carefully controlled. Pain should be controlled with narcotics.

Secondary cerebral ischemia from vasospasm develops in one-third of patients 5–15 days after bleed onset, may persist up to 2 weeks and can produce an infarction. Arterial vasospasm (reversible narrowing of a cerebral vessel) is often detected by CTA even in the absence of cerebral ischemia symptoms. Nevertheless, to minimize the effects of vasospasm, daily administration of a calcium channel blocker, nimodipine, from bleeding onset produces a modest reduction in secondary ischemia and improves outcome.

Rebleeding from the aneurysm is a serious problem. Rebleeding within 24 h of initial bleed occurs in 15%. After survival of 1 day, one-third of patients will rebleed over the next 4 weeks with the daily risk of bleeding being 1–2%. The optimal treatment approach depends on the clinical status of the patient and location and shape of the aneurysm. Aneurysms come in several forms: balloon-like with a narrow stalk; broad stalk; or cylindrical with no stalk. The surgeon is often faced with a dilemma. Operating on a comatose patient with vasospasm is technically difficult and carries a considerable surgical risk of death. However, waiting 1–2 weeks for the vasospasm to reduce and the patient to clinically improve carries the increased risk of the aneurysm rebleeding. In recent years, endovascular techniques enable placement of a detachable spring coil into the aneurysm via an arterial catheter with the goal of tightly packing the aneurysm with coils, effectively closing off blood flow into the aneurysm and thus preventing its rupture. Because endovascular surgery does not require a craniotomy and can be performed on sicker patients, outcomes of endovascularly-coiled patients have had better outcomes than direct surgical clipping in these sicker patients.

Unfortunately, the prognosis of a ruptured saccular aneurysm remains poor. Overall, 50% survive the first 30 days. Of those that survive, another half experience a diminished quality of life and are left with considerable neurologic sequelae that may include cognitive impairment and anosmia. Poor prognostic signs include grades 4 or 5 on the aneurysm grading scales, scores of 3–6 on Glasgow coma scale, presence of intracerebral hematoma, development of hydrocephalus, and rebleeding.

With more patients undergoing a cranial CT or MRI for other indications, patients are being identified with asymptomatic aneurysms. The question then arises as to the risk of future rupture

and whether to electively occlude the aneurysm by craniotomy or arterial endoscopy. While the patient makes the final decision, most experts recommend for aneurysms less than 7–10 mm diameter, periodic CTA to follow the aneurysm and elective surgical clipping if aneurysm expands in size.

Video Legend

This video shows a 53 year-old woman s/p right middle cerebral artery stroke.

Segment 1: Cranial Nerve Exam
- Upper motor neuron facial weakness with lower face affected and normal strength in eyelid and forehead muscles.
- With a central lesion, weakness of trapezius but preserved ipsilateral sternocleidomastoid strength due to bilateral innervation.

Segment 2: Motor Exam
- Pyramidal weakness: upper extremity with extensor > flexor weakness
- Pyramidal weakness: lower extremity with flexor > extensor weakness

Segment 3: Sensory Exam
- Extinction to double simultaneous sensory stimulation
- Extinction to double simultaneous visual stimulation

Segment 4: Reflex Exam
- Hyperreflexia of left upper extremity with clonus at finger flexors
- Hoffman's reflex showing flexion of thumb with "flicking" the terminal phalanx of middle finger
- Spontaneous Babinski sign

Segment 5: Gait Exam
- Stiff hemiparetic gait with extension at knee and hip

Recommended Reading

Davis SM, Donnan GA. Secondary prevention after ischemic stroke or transient ischemic attack. N Eng J Med 2012;366:1914–22. (Current review of methods to prevent strokes)

Furie KL, et al. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack. Stroke 2011;42:227–6. (Current excellent guidelines from American Heart Association/American Stroke Association)

Arboix A, Marti-Vilalta JL. Lacunar stroke. Expert Rev Neurother 1009;9:179–96. (Comprehensive review of lacunar strokes)

Viswanathan A, Greenberg SM. Cerebral amyloid angiopathy in the elderly. Ann Neurol 2011;70:871–80. (Good review of a complicated topic)

Quereshi AI, Mendelow AD, Hanley DF. Intracranial haemorrhage. Lancet 2009;373:1632–44. (Comprehensive review)

van Gijn J, Kerr RS, Rinkel GJE. Subarachnoid haemorrhage. Lancet 2007;36:306–18. (Good review with focus on aneurysms)

Connolly ES Jr, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage. Stroke 2012;43:1711–37. (Current excellent guidelines from American Heart Association/American Stroke Association)