

65 Ischemic Cerebrovascular Disease

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EPIDEMIOLOGY AND RISK FACTORS

There are approximately 795,000 new or recurrent strokes annually in the United States (US) (610,000 being first events and 185,000 being recurrent events) (Go et al., 2014). Some 88% of these strokes are ischemic and 8% to 12% of ischemic strokes result in death within 30 days. On average, every 40 seconds someone in the United States has a stroke. Despite gradual declines in overall stroke death rates in many industrialized countries, stroke remains a leading cause of death and disability, in the United States and worldwide. Stroke mortality is particularly high in Eastern Europe and Asia (World Health Organization, 2004). By 2020, 19 of 25 million annual stroke deaths will be in developing countries (Lemogoum et al., 2005). Of those that survive, approximately 30% require assistance with activities of daily living, 20% require assistance with ambulation, and 16% require institutional care.

Steep decreases in stroke incidence and mortality have occurred in industrialized nations. The reduction in stroke mortality in the United States has been attributed to a declining stroke incidence, and lower case-fatality rates, with suggestive evidence favoring a trend in declining stroke severity. However, the declining stroke incidence has been reversing with the aging of the population, greater awareness of stroke symptoms, and better diagnostic tools. Furthermore, despite a decrease in mortality in developed countries, stroke mortality and incidence are increasing in developing nations. Socioeconomic factors, dietary and lifestyle behaviors, different patterns of risk factors, and environmental conditions may explain the different incidences of stroke observed in different parts of the world.

Factors that may be classified as modifiable and non-modifiable increase the risk for ischemic stroke (Table 65.1). Nonmodifiable risk factors for stroke include older age, male gender, ethnicity, family history, and prior history of stroke. Modifiable risk factors may be subdivided into lifestyle and behavioral risk factors and nonlifestyle factors. Modifiable

TABLE 65.1 Risk Factors for Ischemic Stroke

Nonmodifiable	Modifiable
Age	Arterial hypertension
Gender	Transient ischemic attacks
Race/ethnicity	Prior stroke
Family history	Asymptomatic carotid bruit/stenosis
Genetics	Cardiac disease Aortic arch atheromatosis Diabetes mellitus Dyslipidemia Cigarette smoking Alcohol consumption Increased fibrinogen Elevated homocysteine Lack of physical activity Low serum folate Elevated antiscardiolipin antibodies Oral contraceptive use Obesity

lifestyle factors include lack of physical activity, cigarette consumption, alcohol abuse and illicit drug use. Nonlifestyle factors include low socioeconomic status, arterial hypertension, dyslipidemia, heart disease, and carotid artery disease. Sickle cell disease is also a modifiable nonlifestyle risk factor because exchange therapy can reduce the risk of stroke associated with this disease. Potentially modifiable risk factors (that have yet to be shown to decrease risk when modified, however) include diabetes mellitus (DM), hyperhomocysteinemia, and left ventricular hypertrophy. Less well-documented risk factors include blood markers (e.g., C-reactive protein), ankle-brachial blood pressure ratios, silent cerebral infarcts, white-matter hyperintensities on magnetic resonance imaging (MRI), and degree of carotid artery intima-media thickness. There are also data implicating hemostatic and microcirculatory disorders in stroke as well as circadian and environmental factors.

Risk Factors for Stroke

The incidence of stroke increases dramatically with advancing age, and increasing age is the most powerful risk factor for stroke. The incidence of stroke doubles each decade past 55 years of age. Half of all strokes occur in people older than 75 years. Women have higher stroke case-fatality rates as compared with men. Men age 45–75 develop ischemic strokes at higher rates than women; thereafter, stroke rates are higher in women (Go et al., 2014). With an estimated 20% of the population being older than 65, greater than 10 million octogenarians, and an increasing life expectancy in the United States, it is predicted that the annual number of strokes will reach 1 million by the middle of the twenty-first century. Compared to whites, African Americans have approximately a twofold increased risk of first-ever stroke. The rate of cerebral infarction is higher in African Americans and Hispanic Americans than in whites; this could be partially explained by the higher prevalence of DM and arterial hypertension experienced by these groups. African Americans may have higher rates of intracranial atherosclerotic occlusive disease compared with whites, but this may actually reflect ascertainment bias. Furthermore, the stroke incidence and case fatality rates are also markedly different among the major ethnic groups in Auckland, New Zealand. Maori and Pacific Islands people have a higher rate of mortality within 28 days of stroke when compared with Europeans, especially men. Chinese, Koreans, and Japanese

also may have increased rates of intracranial hemorrhage and intracranial atherosclerotic cerebrovascular disease compared to whites. In comparison with the United States and Western Europe, where hemorrhagic stroke represents 20% or less of all stroke subtypes, 40% of the stroke subtypes are hemorrhagic (intracerebral or subarachnoid hemorrhage) in Japan. Conversely, in India, where ischemic stroke accounts for 80% of all strokes, 10% to 15% of strokes occur in people younger than 40 years and are mostly related to intracranial atherosclerosis.

Heredity and Risk of Stroke

An increased risk is seen with a family history of stroke among first-degree relatives. Genetic factors have been linked with ischemic stroke, but specific genetic variants remain largely unknown (Chinnery et al., 2010). There are a number of genetic causes of stroke. Some inherited diseases, such as the hereditary dyslipoproteinemias, predispose to accelerated atherosclerosis. A number of inherited diseases are associated with nonatherosclerotic vasculopathies, including Ehlers-Danlos (especially type IV) syndrome, Marfan syndrome, Rendu-Osler-Weber disease, and Sturge-Weber syndrome. Familial atrial myxomas, hereditary cardiomyopathies, and hereditary cardiac conduction disorders are examples of inherited cardiac disorders that predispose to stroke. Deficiencies of protein C and S or antithrombin (AT) are examples of inherited hematological abnormalities that can cause stroke. Finally, rare inherited metabolic disorders that can cause stroke include mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS), Fabry disease, and homocystinuria. The presence of the apolipoprotein epsilon-2 allele in elderly individuals and deletion of the gene for the angiotensin-converting enzyme may increase the risk for stroke, but the association with stroke subtype is unclear. The Siblings With Ischemic Stroke Study (SWISS) has demonstrated a relationship between age and stroke in probands and sibs, and the lack of a tight association among ischemic stroke subtypes (Adams Jr. et al., 1993) within families (Meschia et al., 2005, 2006; Wiklund et al., 2007).

Common Modifiable Risk Factors

At least 25% of the adult population has *arterial hypertension*, defined as systolic blood pressure (SBP) greater than or equal to 140 mm Hg or diastolic blood pressure (DBP) greater than or equal to 90 mm Hg. According to the 7th Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of Hypertension (JNC7), *prehypertension* is defined as SBP between 120 and 139 mm Hg or DBP between 80 and 89 mm Hg (Chobanian et al., 2003). Similar guidelines have been developed by the *European Society of Hypertension–European Society of Cardiology Guidelines Committee* (2003). The report from the Eighth Joint National Committee (JNC8) (Table 65.2) recommends treatment of a blood pressure goal of SBP less than 150 mm Hg and DBP less than 90 mm Hg in patients greater than or equal to 60 years old without DM and chronic kidney disease and SBP less than 140 mm Hg and DBP 90 mm Hg in all other adults greater than or equal to 18 years (James et al., 2014). Unfortunately, arterial hypertension remains poorly treated worldwide, and in the United States many patients are either undertreated or untreated. Arterial hypertension predisposes to ischemic stroke by aggravating atherosclerosis and accelerating heart disease, increasing the relative risk for stroke an estimated three- to fourfold. The risk is greater for patients with isolated systolic hypertension and elevated pulse pressure. Arterial hypertension is also the most important

TABLE 65.2 JNC 8 Report: Management of High Blood Pressure in Adults

Population		Goal blood pressure	Agents
Nonblack	Age ≥ 60 years	SBP <150 DBP <90	Thiazide-type diuretic, ACE-I or ARB, or CCB, alone or in combination
	Age < 60 years	SBP < 140	
	All ages	DBP < 90	
	Diabetes present No chronic kidney disease		
Black	Age ≥ 60 years	SBP <150 DBP <90	Thiazide-type diuretic or CCB, alone or in combination
	Age < 60 years	SBP < 140	
	All ages	DBP < 90	
	Diabetes present No chronic kidney disease		
All races	All ages	SBP < 140	ACE-I or ARB, alone or in combination with other drug class
	Chronic kidney disease present with or without diabetes	DBP < 90	

Adapted from James, P.A., Oparil, S., Carter, B.L., et al., 2013. 2014 Evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the eighth Joint National Committee (JNC 8). *JAMA*. Doi:10.1001/jama.2013.284427, E1-E14, published online December 18, 2013. Accessed 1/14/2014.

ACE-I, Angiotensin-converting enzyme inhibitor; ARB, angiotensin II type 1 receptor blocker; BB, beta-blocker; CCB, calcium-channel blocker; DBP, diastolic blood pressure; SBP, systolic blood pressure.

modifiable risk factor for stroke and the most powerful risk factor for all forms of vascular cognitive impairment. Lowering blood pressure in stroke survivors helps prevent recurrent stroke and is more important than the specific agent used, although there is some suggestion that beta-blockers are less preferred than other agents based on meta-analyses (Lindholm et al., 2005). Blood pressure treatment that results in a modest reduction in SBP of 10 to 12 mm Hg and 5 to 6 mm Hg diastolic is associated with a 38% reduction in stroke incidence (MacMahon and Rodgers, 1996). Treatment of isolated systolic hypertension in the elderly is also effective for reducing stroke risk. The Systolic Hypertension in the Elderly Program showed a 36% reduction in nonfatal plus fatal stroke over 5 years in the age 60-and-older group when isolated systolic hypertension was treated. Treating systolic hypertension also slows the progression of carotid artery stenosis. The PROGRESS trial evaluated the effects of perindopril and indapamide on the risk for stroke in patients with histories of stroke or transient ischemic attack (TIA). Regardless of blood pressure at entry, patients clearly benefited from treatment (PROGRESS Collaborative Group, 2001).

About 171 million people worldwide have type 2 DM, including 18 million Americans. It is estimated that these numbers will grow to 366 million people worldwide and 30 million Americans by 2030. Diabetes mellitus increases the risk of ischemic cerebrovascular disease an estimated two- to fourfold as compared with the risk in people without diabetes. In addition, DM increases morbidity and mortality after stroke. Macrovascular disease is the leading cause of death among patients with DM. The mechanisms of stroke secondary to diabetes may be caused by cerebrovascular atherosclerosis, cardiac embolism, or rheological abnormalities. The

excess stroke risk is independent of age or blood pressure status. Diabetes associated with arterial hypertension adds significantly to stroke risk. There is a fourfold increase in the relative risk of cardiovascular events among patients with diabetes and hypertension compared to those without the two conditions. Diabetic persons with retinopathy and autonomic neuropathy appear to be a group at particularly high risk for ischemic stroke. High insulin levels increase the risk for atherosclerosis and may represent a pathogenetic factor in cerebral small-vessel disease. Presently, no evidence exists that tighter diabetic control or normalizing HbA_{1c} levels over time decreases the risk for stroke or stroke recurrence.

High total cholesterol and high low-density lipoprotein (LDL) concentration are correlated with atherosclerosis. Dyslipidemia is a recognized risk factor for ischemic stroke. Meta-analyses have suggested that ischemic stroke risk increases with increasing serum cholesterol, and the reduction in stroke risk associated with 3-hydroxy 3-methylglutaryl coenzyme A reductase inhibitor (statin) therapies is related to reduction in LDL cholesterol (Amarencu et al., 2004; Tirschwell et al., 2004). Lipid-modifying therapy with statins has definitively established that reduction of LDL cholesterol reduces cardiovascular risk. Statins benefit stroke survivors as well. Lipid-lowering agents may slow progression of atherosclerotic plaque growth and may cause a regression in rate of plaque formation.

The Scandinavian Simvastatin Survival Study (4S) (Scandinavian Simvastatin Survival Study Group, 1999) investigated cholesterol lowering in persons with coronary heart disease and hypercholesterolemia and found a reduction in the total mortality rate, major coronary events, and number of cardiac revascularization procedures. Post hoc analysis also showed a 28% reduction in fatal or nonfatal stroke and TIAs (Pedersen et al., 1998). The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) study investigated cholesterol lowering with pravastatin in patients with a previous myocardial infarction (MI) or unstable angina who had cholesterol levels between 155 and 271 mg/dL and reported a remarkable reduction in MI, cardiac revascularizations, and cardiovascular deaths, as well as a 20% reduction in the risk for stroke (Long-Term Intervention with Pravastatin in Ischaemic Disease [LIPID] Study Group, 1998). Similar findings were associated with atorvastatin in the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial and the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA) studies. MIRACL showed a 50% relative risk reduction (RRR) ($P = 0.045$) in stroke among high-risk coronary disease patients (Schwartz et al., 2001). The ASCOT-LLA study demonstrated a favorable trend for fatal and nonfatal stroke, with a 27% RRR in patients at low risk for coronary events (hazard ratio, 0.73; 95% confidence interval [CI], 0.56–0.96; $P = 0.0236$), though not to the pre-specified endpoint of $P = 0.01$ (Sever et al., 2003).

Although the Heart Protection Study (HPS) of patients at high risk with DM, coronary artery disease, or other atherosclerotic vascular disease did show an overall reduction in stroke risk, a subgroup analysis of the Heart Protection Study (HPS) did not show a reduction in the risk for stroke among patients with prior cerebrovascular disease (Heart Protection Study Collaborative Group, 2004). This subgroup analysis was limited in that the mean time from event to enrollment was 4.3 years, and the LDL reduction was 38 mg/dL. Subsequently, the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study was published (SPARCL Investigators, 2006). This was a study of 4731 patients who had suffered either a stroke or TIA, had no known coronary heart disease, had LDL cholesterol levels of 100 to 190 mg/dL, and who were randomized to placebo or 80 mg of atorvastatin. A 56-mg/dL

reduction in LDL treatment was noted in patients on atorvastatin. During a median follow-up of 4.9 years, 11.2% of atorvastatin-treated patients and 13.1% of placebo patients had a fatal or nonfatal stroke for an adjusted hazard ratio of 0.84 (95% CI, 0.71–0.99). A small increase in hemorrhagic stroke was reported in the atorvastatin group. Moreover, recent studies evaluating withdrawal of statins after acute ischemic stroke showed a higher incidence of death or dependency at 90 days (Blanco et al., 2007). Current guidelines of the American Heart Association (AHA) and proposed modifications of the NCEP-III guidelines suggest that all patients at risk for stroke or who have had a cerebral infarction should be treated to a goal LDL level of below 70 mg/dL (Grundy et al., 2004; Sacco et al., 2006). The most recent American College of Cardiology (ACC)/AHA guidelines recommends that all ischemic stroke and TIA patients should be treated with a statin regardless of the initial LDL (Stone et al., 2014).

Atrial fibrillation, the most common sustained cardiac arrhythmia in the general population, affects about 1% of adults, is the most common cause for cardioembolic stroke, and is a risk factor for future cardiovascular disease. An estimated 1 to 2 million Americans have chronic nonvalvular atrial fibrillation (NVAF), a condition that is associated with an overall risk for stroke of approximately five- to sixfold, and a mortality rate approximately twice that of age- and sex-matched individuals without atrial fibrillation. The prevalence of atrial fibrillation increases with advancing age and is 0.5% for patients aged 50 to 59 years and 8.8% for those aged 80 to 89 years. Approximately 70% of individuals with atrial fibrillation are between 65 and 85 years of age. NVAF is associated with a substantial risk for stroke. Heart failure, arterial hypertension, DM, prior stroke or TIA, and age older than 75 years increase the risk for embolism in patients with NVAF. High-risk patients have a 5% to 7% yearly risk for thromboembolism. The CHADS2 Score represents a validated quantification of risk, with congestive heart failure, hypertension, age older than 75 years, and a history of DM being assigned 1 point; stroke or TIA are assigned 2 points (Gage et al., 2001). Ischemic stroke rates increase from 1.9 to 18.2 events per 100 patient-years with CHADS 2 scores of 0 and 6, respectively. Left atrial enlargement also increases the risk for stroke in men. Likewise, left ventricular hypertrophy as demonstrated by electrocardiography (ECG) in men with pre-existing ischemic heart disease is a major risk factor for stroke. The CHADS2-VASC score for atrial fibrillation stroke risk was significantly better at stratifying patients into risk groups (Olesen et al., 2011).

Cigarette smoking is the leading cause of preventable death in the United States. Cigarette smoking is a major risk factor for coronary artery disease, stroke, and peripheral arterial disease, an independent risk factor for ischemic stroke in men and women of all ages, and a leading risk factor of carotid atherosclerosis in men. The risk for stroke in smokers is two to three times greater than in nonsmokers. The mechanisms of enhanced atherogenesis promoted by cigarette smoking are incompletely understood but include reduced capacity of the blood to deliver oxygen, cardiac arrhythmias, increased blood coagulability, and triggering of arterial thrombosis and arterial spasm. Tobacco also increases carotid artery plaque thickness. More than 5 years may be required before a reduction in stroke risk approaches that of never-smokers after cessation of smoking. Switching to pipe or cigar smoking is of no benefit. Counseling, nicotine replacement products, varenicline (a nicotinic receptor partial agonist), and bupropion are efficacious smoking cessation treatments.

There is a J-shaped association between alcohol consumption and ischemic stroke; light to moderate use (up to two drinks a day for men and one for women) evenly distributed

throughout the week elevates HDL concentration and is associated with reduced risk, whereas heavy alcohol consumption is associated with an increased risk for total stroke. Heavy drinking may precipitate cardiogenic brain embolism. Alcohol consumption increases the risk for hemorrhagic stroke; alcohol-induced hypertension predisposes to spontaneous intracranial hemorrhage. Furthermore, active drinkers have a higher frequency of obstructive sleep apneas (OSA) with more severe hypoxemia. Elimination or reduction of alcohol consumption is recommended for heavy drinkers. Restriction of alcohol consumption to fewer than two drinks daily for men and less than one drink daily for nonpregnant women is recommended for light to moderate drinkers.

The prevalence of obesity (body mass index of 30 or higher) in the United States has increased. More than 61% of adult Americans are overweight, and 27% are obese. Obesity, particularly abdominal, is an important risk factor for cardiovascular disease in men and women of all ages. There is some evidence that physical activity can reduce the risk for stroke. Regular exercise lowers arterial blood pressure, decreases insulin resistance, increases HDL cholesterol, and is associated with lower cardiovascular morbidity and mortality.

Numerous studies have established an association between OSA and stroke; moreover, the severity of OSA is much higher in stroke patients than in controls. Habitual snoring increases the risk for stroke and adversely affects the outcome of patients admitted to the hospital with stroke. Mounting evidence also suggests that inflammation, lipoprotein(a) concentration, impaired fibrinolysis, and increased thrombotic potential are important nontraditional cardiovascular risk factors. Atherosclerotic lesions of the carotid artery bifurcation are a common cause of stroke. Asymptomatic carotid artery disease carries a greater risk for vascular death from coronary artery disease than from stroke. Asymptomatic carotid artery stenosis of less than 75% carries a stroke risk of 1.3% annually; with stenosis of greater than 75%, the combined TIA and stroke rate is 10.5% per year, with most events occurring ipsilateral to the stenosed carotid artery. Plaque composition may be an important factor in the pathophysiology of carotid artery disease. Plaque structure rather than degree of carotid artery stenosis may be a more critical factor in determining stroke risk. Ultrasonographic carotid artery plaque morphology may identify a subgroup of patients at high risk for stroke. Ulcerated, echolucent, and heterogeneous plaques with a soft core represent unstable plaques at high risk for producing thromboembolism. Over 74% of patients with major stroke and ipsilateral carotid stenosis have been shown to have thrombotically active plaque surface characteristics (Spagnoli et al., 2004).

Patients who suffer TIAs are at greater risk than normal controls for stroke or death from vascular causes. The risk for stroke is approximately three times higher. Symptomatic carotid artery stenosis of greater than 70% carries an annual risk for stroke of approximately 15%. Approximately 10% to 15% of those experiencing a stroke have TIAs before their stroke. Patients with hemispheric TIAs are at greater risk for ipsilateral stroke than patients with retinal TIAs. Patients with a first stroke are at greater risk for recurrent stroke, especially (but not exclusively) early after the first stroke. Those who suffer a recurrent stroke have a higher mortality than patients with first stroke. If the recurrence is contralateral to the first stroke, prognosis for functional recovery is poor. The risk for stroke recurrence is also increased by the presence of underlying dementia.

The aorta is the most frequent site of atherosclerosis. Protruding atheroma may be the cause of otherwise unexplained TIAs or strokes. Aortic-arch atheromatosis detected by transesophageal echocardiography is an independent risk factor for cerebral ischemia; the association is particularly strong with

mobile and thick atherosclerotic plaques more than 4 mm in thickness (French Study of Aortic Plaques in Stroke Group, 1996). The prevalence of ulcerated plaques was 16.9% among patients with cerebrovascular diseases, compared to 5.1% among patients with other neurological diseases. Remarkably, ulcerated plaques were found in 61% of cryptogenic cerebral infarcts, compared to 22% of cerebral infarcts with a known cause.

Other Risk Factors for Stroke

Hemostatic factors may be important in assessing the risk for cerebrovascular events. Elevated hematocrit, hemoglobin concentration, and increased blood viscosity may be indicators of ischemic stroke risk. Elevation of plasma fibrinogen is an independent risk factor for the development of cerebral infarction. Epidemiological studies have shown a correlation between elevated plasma fibrinogen levels and both ischemic stroke incidence and mortality. An elevated plasma fibrinogen level may reflect progression of atherogenesis. Plasminogen activator inhibitor-1 excess and factor VII are independent risk factors for coronary heart disease. Compared with white Americans, black Americans have higher mean levels of fibrinogen, factor VIII, von Willebrand factor, and AT, and lower mean levels of protein C. Fibrinogen levels are closely correlated with other stroke risk factors such as cigarette smoking, arterial hypertension, diabetes, obesity, hematocrit levels, and spontaneous echocardiographic contrast. Antiphospholipid (aPL) antibodies are a marker for an increased risk for thrombosis, including TIAs and stroke, particularly in those younger than 50 years. In older patients, the presence of aPL (either lupus anticoagulants [LAs] or anticardiolipin [aCL]) among patients with ischemic stroke does not predict either increased risk for subsequent vascular occlusive events over 2 years or a differential response to aspirin or warfarin therapy. As such, routine screening for aPL in older patients with ischemic stroke does not appear warranted (Levine et al., 2004). Activated protein C resistance due to the factor V Leiden mutation is associated with deep venous thrombosis in otherwise healthy individuals with additional prothrombotic risk factors. An overall association of the factor V Leiden mutation and arterial thrombosis has not been found. As opposed to homozygous mutations, heterozygous factor V Leiden and prothrombin gene mutations have no clear association with increased stroke risk (Fields and Levine, 2005). Elevated von Willebrand factor is a risk factor for MI and ischemic stroke. Elevated levels of fasting total homocysteine (normal 5–15 mM), a sulfhydryl-containing amino acid, have been associated with an increased risk for stroke and thrombotic events in case-controlled studies. Metabolism of homocysteine requires vitamin B₆ (pyridoxine), vitamin B₁₂ (cyanocobalamin), folate, and betaine. Plasma homocysteine concentrations may be reduced by the administration of folic acid alone or in combination with vitamins B₆ and B₁₂. Conversely, serum folate concentrations of 9.2 nM or less have been associated with elevated plasma levels of homocysteine, and a decreased folate concentration alone may be a risk factor for ischemic stroke, particularly among blacks. However, folic acid supplementation does not have a major impact on stroke reduction (Lee et al., 2010).

Stroke is uncommon among women of childbearing age. The relative risk for ischemic stroke is increased among users of high-dose estrogen oral contraceptives, particularly with coexistent arterial hypertension, cigarette smoking, and increasing age. Based on an odds ratio of 1.93, the incidence is increased to 8.5/100,000, which translates into a number needed to harm of 24,000 women to cause one ischemic stroke (Gillum et al., 2000). Thus, for a healthy young woman without any other stroke risk factors, the risk of stroke associ-

ated with oral contraceptives is small and probably outweighed by their benefits. New agents containing lower doses of estrogen and progestin have reduced the frequency of oral contraceptive-related cerebral infarction. Two postmenopausal hormone replacement studies with equine estrogen (Premarin) showed no benefit in reducing the incidence of stroke in a cohort of women with coronary heart disease (Hulley et al., 1998). The Women's Estrogen for Stroke Treatment study of estradiol replacement in postmenopausal women status post stroke also failed to show a reduction in recurrent stroke (Viscoli et al., 2001). In addition, the Women's Health Initiative, a prospective randomized trial of estrogen therapy in healthy postmenopausal women, was halted prematurely because the risks outweighed the benefits. Absolute excess risks per 10,000 person-years attributable to estrogen plus progestin were sevenfold for coronary heart disease events, eightfold for strokes, eightfold for pulmonary thromboembolism, and eightfold for invasive cancers, whereas absolute risk reductions per 10,000 person-years were sixfold for colorectal cancers and fivefold for hip fractures (Rossouw et al., 2002). The risk for thrombosis associated with pregnancy is high in the postpartum period. The risk for cerebral infarction is increased in the 6 weeks after delivery but not during pregnancy.

A diurnal and seasonal variation of ischemic events occurs. Circadian changes in physical activity, catecholamine levels, blood pressure, blood viscosity, platelet aggregability, blood coagulability, and fibrinolytic activity may explain the circadian variations in onset of myocardial and cerebral infarction. An early-morning peak occurs for all subtypes of stroke. Rhythmometric analyses support the notion that stroke is a chrono-risk disease, in which cold temperatures also represent a risk factor. A history of recent infection, particularly of bacterial origin and within 1 week of the event, is also a risk factor for ischemic stroke in patients of all ages. A number of reports suggest that *Chlamydia pneumoniae*, a causative organism of respiratory infections, may have a role in carotid and coronary atherosclerosis. Some studies have also identified an association with chronic infections with *Helicobacter pylori* and cytomegalovirus. These findings have not been confirmed, however.

PATHOPHYSIOLOGY OF CEREBRAL ISCHEMIA

Except for the lack of an external elastica lamina in the intracranial arteries, the morphological structure of the cerebral vessels is similar to those in other vascular beds. The arterial wall consists of three layers: the outer layer, or adventitia; the middle layer, or media; and the inner layer, or intima. The intima is a smooth monolayer of endothelial cells providing a nonthrombotic surface for blood flow. One of the major functions of the endothelium is active inhibition of coagulation and thrombosis.

The brain microcirculation comprises the smallest components of the vascular system, including arterioles, capillaries, and venules. The arterioles are composed primarily of smooth-muscle cells around the endothelial-lined lumen and are the major sites of resistance to blood flow in the arterial tree. The capillary wall consists of a thin monolayer of endothelial cells. Nutrients and metabolites diffuse across the capillary bed. The venules are composed of endothelium and a fragile smooth-muscle wall and function as collecting tubules. The cerebral microcirculation distributes blood to its target organ by regulating blood flow and distributing oxygen and glucose to the brain, while removing byproducts of metabolism.

A cascade of complex biochemical events occurs seconds to minutes after cerebral ischemia. Cerebral ischemia is caused by reduced blood supply to the microcirculation. Ischemia

causes impairment of brain energy metabolism, loss of aerobic glycolysis, intracellular accumulation of sodium and calcium ions, release of excitotoxic neurotransmitters, elevation of lactate levels with local acidosis, free radical production, cell swelling, overactivation of lipases and proteases, and cell death. Many neurons undergo apoptosis after brain ischemia. Ischemic brain injury is exacerbated by leukocyte infiltration and development of brain edema. These biochemical changes have been the targets for many agents and strategies aimed at neuroprotection after cerebral infarction.

Complete interruption of cerebral blood flow causes suppression of the electrical activity within 12 to 15 seconds, inhibition of synaptic excitability of cortical neurons after 2 to 4 minutes, and inhibition of electrical excitability after 4 to 6 minutes. Normal cerebral blood flow at rest in the normal adult brain is approximately 50 to 55 mL/100 g/min, and the cerebral metabolic rate of oxygen is 165 mmol/100 g/min. There are certain ischemic thresholds in experimental focal brain ischemia. When blood flow decreases to 18 mL/100 g/min, the brain reaches a threshold for electrical failure. Although these neurons are not functioning normally, they do have the potential for recovery. The second level, known as the *threshold of membrane failure*, occurs when blood flow decreases to 8 mL/100 g/min. Cell death can rapidly result. These thresholds mark the upper and lower blood-flow limits of the ischemic penumbra. The ischemic penumbra, or area of "misery perfusion," is the area of the ischemic brain between these two flow thresholds in which there are some neurons that are functionally silent but structurally intact and potentially salvageable.

PATHOLOGY OF ISCHEMIC STROKE

The pathological characteristics of ischemic stroke depend on the mechanism of stroke, the size of the obstructed artery, and the availability of collateral blood flow. There may be advanced changes of atherosclerosis visible within arteries. The surface of the brain in the area of infarction appears pale. With ischemia caused by hypotension or hemodynamic changes, the arterial border (or watershed) zones are most vulnerable. A wedge-shaped area of infarction in the center of an arterial territory may result if there is occlusion of a main artery in the presence of collateral blood flow. In the absence of collateral blood flow, the entire territory supplied by an artery may be infarcted. With occlusion of a major artery such as the internal carotid, there may be a multilobar infarction. There may be evidence of flattening of the gyri and obliteration of the sulci caused by cerebral edema. A lacunar infarction with a size of 1.5 cm or less in subcortical areas or in the brainstem may be barely visible in the macroscopic analysis of the cut brain. Small emboli to the brain tend to lodge at the junction between the cerebral cortex and the white matter. Reperfusion of the infarct may occur when the clot lyses, leading to hemorrhagic transformation.

The microscopic changes after cerebral infarction are well documented. The observed changes depend on the age of the infarction. The changes do not occur immediately and may be delayed up to 6 hours after the infarction. There is neuronal swelling initially, which is followed by shrinkage, hyperchromasia, and pyknosis. Chromatolysis appears, and the nuclei become eccentric. Swelling and fragmentation of the astrocytes and endothelial swelling occur. Neutrophil infiltrates appear as early as 4 hours after the ischemia and become abundant by 36 hours. Within 48 hours, the microglia proliferate and ingest the products of myelin breakdown and form foamy macrophages. Later there is neovascularity with proliferation of capillaries and increased prominence of the existing capillaries. The elements in the area of necrosis are gradually

reabsorbed, and a cavity consisting of glial and fibrovascular elements forms. In a large infarction, there are three distinct zones: an inner area of coagulative necrosis; a middle zone of vacuolated neuropil, leukocytic infiltrates, swollen axons, and thickened capillaries; and an outer marginal zone of hyperplastic astrocytes and variable changes in nuclear staining.

CLINICAL SYNDROMES OF CEREBRAL ISCHEMIA

A number of syndromes result from ischemia involving the central nervous system (CNS) (Brazis et al., 2011).

Transient Ischemic Attacks

An estimated 400,000 individuals experience a TIA each year in the US. The true frequency of TIA may be far greater due to under-reporting of TIA-like events. The 2014 AHA statistical update suggested that there may be as many as 5 million possible TIAs annually in the US (Go et al., 2014).

A TIA is a prognostic indicator of stroke, with one-third of untreated TIA patients having a stroke within 5 years. About 1 in 10 patients with TIA experience a stroke in the next 3 months. The interval from the last TIA is an important predictor of stroke risk; of all patients who subsequently experience stroke, 21% do so within 1 month and 51% do so within 1 year of the last TIA. In one series, patients with TIA had a 3-month stroke risk of 10.5%, equal to the recurrence rate following a stroke. Furthermore, 50% of those strokes occurred within 48 hours of TIA onset (Johnston et al., 2000). Cardiac events are the principal cause of death in patients who have had a TIA. The 5% to 6% annual mortality rate after TIA is mainly caused by MI.

A TIA is a temporary and "nonmarching" neurological deficit of sudden onset; attributed to focal ischemia of the brain, retina, or cochlea; and lasting less than 24 hours. Yet most TIAs last only a few minutes. Episodes that last longer than 1 hour are usually due to small infarctions. With the advent of diffusion-weighted magnetic resonance imaging (DW-MRI) sequences, the time-based definition of TIA is inadequate because infarctions are frequently evident on DW-MRI in patients whose clinical manifestations resolved completely within a few hours. Thus, a "tissue-based" modification of the TIA definition has been proposed, suggesting that any transient episode, regardless of duration, associated with a clinically appropriate lesion by MRI be defined as a stroke, and that otherwise prolonged events (>1–6 hours in duration) be defined as stroke rather than TIA when otherwise clinically appropriate (Albers et al., 2002). Furthermore, DW-MRI is useful in predicting the risk for early stroke; patients with TIA and DW-MRI lesions are at greater risk for experiencing a subsequent stroke than patients without a lesion (Coutts et al., 2005). Johnston et al. developed a risk stratification score in patients with TIAs, known as the *ABCD2 score*. The ABCD2 score is based on age, blood pressure ($\geq 140/90$ mm Hg), clinical features, TIA duration, and diabetes (Table 65.3). ABCD2 scores of 4 or greater indicate a moderate to high stroke risk and justify prompt hospital admission (Johnston et al., 2007).

The onset of TIA symptoms is sudden, reaching maximum intensity almost immediately. To qualify as a TIA, therefore, an episode should also be followed by complete clinical recovery. TIAs involving the carotid circulation should be distinguished from those involving the vertebrobasilar circulation. Headaches often occur in patients with TIAs. As such, migraine with aura may sometimes be indistinguishable from TIA.

Agreement between physicians to define the likelihood of a TIA, even among fellowship-trained neurologists, remains poor (Castle et al., 2010). The following symptoms are

TABLE 65.3 ABCD2 Score

Age 60 or older	1 point
Blood pressure $\geq 140/90$	1 point
Clinical:	
Unilateral weakness	2 points
Speech impairment	1 point
Duration:	
60 minutes or more	2 points
<60 minutes	1 point
Diabetes mellitus	1 point

BOX 65.1 Recognition of Carotid and Vertebrobasilar Transient Ischemic Attacks**SYMPTOMS SUGGESTIVE OF CAROTID TRANSIENT ISCHEMIC ATTACKS**

Transient ipsilateral monocular blindness (amaurosis fugax)
 Contralateral body weakness or clumsiness
 Contralateral body sensory loss or paresthesias
 Aphasia with dominant hemisphere involvement
 Various degrees of contralateral homonymous visual field defects
 Dysarthria (not in isolation)

SYMPTOMS SUGGESTIVE OF VERTEBROBASILAR TRANSIENT ISCHEMIC ATTACKS

Usually bilateral weakness or clumsiness but may be unilateral or shifting
 Bilateral, shifting, or crossed (ipsilateral face and contralateral body) sensory loss or paresthesias
 Bilateral or contralateral homonymous visual field defects or binocular vision loss
 Two or more of the following symptoms: vertigo, diplopia, dysphagia, dysarthria, and ataxia

SYMPTOMS NOT ACCEPTABLE AS EVIDENCE OF TRANSIENT ISCHEMIC ATTACK

Syncope, dizziness, confusion, urinary or fecal incontinence, and generalized weakness
 Isolated occurrence of vertigo, diplopia, dysphagia, ataxia, tinnitus, amnesia, drop attacks, or dysarthria

considered typical of TIAs in the carotid circulation: ipsilateral amaurosis fugax, contralateral sensory or motor dysfunction limited to one side of the body, aphasia, contralateral homonymous hemianopia, or any combination thereof. The following symptoms represent typical TIAs in the vertebrobasilar system: bilateral or shifting motor or sensory dysfunction, complete or partial loss of vision in the homonymous fields of both eyes, or any combination of these symptoms. Perioral numbness also occurs. Isolated diplopia, vertigo, dysarthria, and dysphagia should not be considered as being caused by a TIA unless they occur in combination with one another or with any of the other symptoms just listed (Box 65.1). Older patients with isolated vertebrobasilar symptoms and a significant history of cardiovascular risk factors should, however, be evaluated for possible TIA or stroke, because they are at substantially higher risk for cerebrovascular events (Norving et al., 1995).

Occlusive disease in the subclavian arteries or the innominate artery can give rise to extracranial steal syndromes. The most well-defined syndrome is subclavian steal syndrome

(SSS). In SSS, reversal of flow in the vertebral artery is caused by a high-grade subclavian artery stenosis or occlusion proximal to the origin of the vertebral artery from the aortic arch or innominate artery, with resultant symptoms of brainstem ischemia, usually precipitated by actively exercising the ipsilateral arm. The left side is involved most frequently. With innominate artery occlusion, the origin of the right carotid is also subject to reduced perfusion pressure. Subclavian artery or innominate artery stenosis can be suspected by a reduced or delayed radial pulse and diminished blood pressure in the affected arm relative to the contralateral arm. A subclavian steal may be symptomatic or asymptomatic. Many patients have angiographic evidence of reversed vertebral blood flow without ischemic symptoms. Transcranial Doppler ultrasonography may detect transient retrograde basilar blood flow during an ischemic forearm challenge. Retrograde vertebral artery flow is a benign entity. Brainstem infarction is an uncommon complication of the subclavian steal syndrome.

Transient global amnesia (TGA) is characterized by a reversible antegrade and retrograde memory loss, except for a total amnesia of events that occur during the attacks and inability to learn newly acquired information. During the attacks, patients remain alert without motor or sensory impairments and often ask the same questions repeatedly. Patients are able to retain personal identity and carry on complex activities. TGA most commonly affects patients 50 years and older. Men are affected more commonly than women. The attacks begin abruptly without warning. A typical attack lasts several hours (mean, 3–6 hours) but seldom longer than 12 hours. Onset of TGA may follow physical exertion, sudden exposure to cold or heat, or sexual intercourse. Although many conditions have been associated with transient episodes of amnesia, in most instances TGA is of primary or unknown cause. TGA has been associated with epilepsy, migraine, intracranial tumors, overdose of diazepam, cardiac arrhythmias secondary to digitalis intoxication, and as a complication of cerebral and coronary angiography. Many reports have suggested a vascular causal factor. Bilateral hippocampal and parahippocampal complex ischemia in the distribution of the posterior cerebral arteries or cortical spreading depression of migrainous origin in these areas are potential mechanisms. Acute confusional migraines in children and TGA have a number of similar features. Others have suggested an epileptic causal factor for a minority of patients. Venous hypertension with transient hypoxemia in the context of incompetent internal jugular vein valves has also been suggested as a possible mechanism for TGA (Neddelmann et al., 2005). Transient amnesias have been divided into pure TGA, probable epileptic amnesia, and probable transient ischemic amnesia. In contrast to patients with TIAs, the prognosis of persons with pure TGA is benign, with no apparent increased risk for vascular endpoints. Recurrences are uncommon. Extensive evaluations are not usually required except to distinguish TGA from TIA or seizures. Treatment with platelet antiaggregants is not indicated in most patients unless there is a suspicion for transient ischemic amnesia. The use of prophylactic calcium channel blockers may be justified in patients with a potential migrainous causal factor.

Drop attacks are characterized by the sudden loss of muscle tone and strength. The attacks cause the patients to unexpectedly fall to the ground. Consciousness is preserved. Most attacks occur while standing or walking and often follow head or neck motion. Drop attacks have been considered a symptom of vertebrobasilar ischemia, but many of these patients have other coexistent disorders that could otherwise explain their symptoms. In rare instances, drop attacks may indeed be caused by ischemia of the corticospinal tract or reticular formation. However, isolated drop attacks are seldom a manifestation of vertebrobasilar occlusive disease. In most instances

these attacks are secondary to akinetic seizures, high cervical spine or foramen magnum lesions, postural hypotension, Tumarkin otolithic crises (in Ménière disease), or near syncope of cardiac origin.

Transient ischemic attacks may result from atherothromboembolism that originates from ulcerated extracranial arteries, emboli of cardiac origin, occlusion of small penetrating arteries that arise from the large surface arteries of the circle of Willis, altered local blood flow (perfusion failure) due to severe arterial stenosis, nonatherosclerotic vasculopathies, or hypercoagulable states. Preceding TIAs occur frequently in patients with brain infarction. In published series, TIAs occurred before 25% to 50% of atherothrombotic infarcts, in 11% to 30% of cardioembolic infarcts, and in 11% to 14% of lacunar infarcts. Lacunar TIAs in general share the same pathogenetic mechanisms of lacunar infarcts and are associated with a substantially better prognosis than nonlacunar TIAs.

Crescendo episodes of cerebral ischemia that increase in frequency, severity, or duration must be treated as neurological emergencies. One small subset of crescendo TIAs is represented by the *capsular warning syndrome*, characterized by restricted, stereotyped, repeated episodes of capsular ischemia causing contralateral symptoms involving the face, arm, and leg. Occasionally, "stuttering TIAs" may be confused with epileptic events. When capsular infarction develops, it is usually a lacunar-type stroke and involves a single penetrating vessel. Occasionally, striatocapsular or anterior choroidal artery territory infarction occurs. These may be lacunar in origin but sometimes are associated with carotid artery steno-occlusive disease. Typically these patients are refractory to conventional forms of therapy.

Rational treatment of patients with TIAs depends on a careful history and detailed physical examination. The neurovascular examination may disclose a well-localized bruit in the mid- or upper cervical area. Bruits arise when normal laminar blood flow is disturbed. However, the presence of a cervical bruit does not necessarily indicate underlying carotid artery atherosclerosis. Correlation with angiography or ultrasound studies shows only a 60% concordance with cervical auscultation in predicting the presence of arterial stenosis. Radiated cardiac murmurs, hyperdynamic states, nonatherosclerotic carotid arterial lesions, and venous hums can produce cervical murmurs. The absence of a bruit has little diagnostic value; the bruit may disappear when the stenosis is advanced. Conversely, a cervical bruit may be heard contralateral to an internal carotid artery occlusion or reflect ipsilateral external carotid artery disease of uncertain clinical significance.

Different types of microemboli (e.g., cholesterol crystals, platelet fibrin, calcium, and other forms of debris) can be seen in the retinal arterioles during or between attacks of transient monocular visual loss. Engorgement of conjunctival and episcleral vessels, corneal edema and rubeosis irides, and anterior-chamber cell flares are indicative of an underlying ischemic oculopathy. Asymmetrical hypertensive retinal changes noted on funduscopy are suggestive of a high-grade carotid artery stenosis or occlusion on the side of the less severely involved retina. Venous stasis retinopathy may occur with high-grade carotid artery stenosis or occlusion and is characterized by diminished or absent venous pulsations, dilated and tortuous retinal veins, peripheral microaneurysms, and blossom-shaped hemorrhages in the midperipheral retina. Retinal microvascular abnormalities correlate with an increased incidence of lacunar strokes (Yatsuya et al., 2010). Corneal arcus senilis may be less obvious or absent on the side of low perfusion.

Many conditions can resemble a TIA. Subdural, intracerebral, or subarachnoid hemorrhage, space-occupying lesions, seizures, hypoglycemia, migraine, syncope, and labyrinthine disorders are among the diverse conditions in the differential

diagnosis when TIA is considered. Symptoms of a transient neurological dysfunction that resolve incompletely should lead the physician to question the diagnosis of TIA. Similarly, a migration or "march of symptoms" from one part of the body to another is rare during a TIA and more indicative of a focal seizure or migraine. Fortification phenomena or scintillating bright visual symptoms are suggestive of migraine. In rare instances, involuntary limb-shaking movements can occur, but in general, involuntary movements reflect convulsive activity rather than a TIA.

Carotid Artery System Syndromes

Carotid Artery Syndromes

Amaurosis fugax may be described as a sudden onset of transient monocular visual loss. A curtain or shade pattern with the loss of vision moving superiorly to inferiorly is described only in 15% to 20% of patients. Less commonly, a concentric vision loss, presumed to be caused by diminished blood flow to the retina, is described. Most attacks are spontaneous and unrelated to positional changes. The vision loss is often brief and painless. The duration of vision loss is usually 1 to 5 minutes and rarely lasts more than 30 minutes. After an episode of amaurosis fugax, the vision is usually fully restored, although some patients may have permanent vision loss caused by a retinal infarction (see Chapters 16 and 17).

Middle Cerebral Artery Syndromes

Amaurosis fugax is the sole feature that distinguishes the carotid artery syndrome from a middle cerebral artery (MCA) syndrome. An MCA infarction is one of the most common manifestations of cerebrovascular disease. The clinical picture with an MCA infarction varies and depends on whether the site of the occlusion is in the stem, superior division, inferior division, or lenticulostriate branches, and the extent of collateral blood flow.

When the stem of the MCA is occluded, there is usually a large hemispheric infarction with contralateral hemiplegia, conjugate eye deviation toward the side of the infarct, hemianesthesia, and homonymous hemianopia. Associated global aphasia occurs if the dominant hemisphere is involved, and hemineglect with nondominant hemispheric lesions. The difference between an upper-division MCA infarction and an MCA stem lesion is that the hemiparesis usually affects the face and arm more than the leg with upper division infarction. A Broca-type aphasia is more common in upper-division infarcts of the dominant hemisphere because of the preferential involvement of the anterior MCA branches. Impaired language prosody may be seen with anterior nondominant hemisphere MCA infarcts. With lower-division MCA syndromes, a Wernicke-type aphasia is seen with dominant hemisphere infarction and behavioral disturbances are seen with nondominant infarction. A homonymous hemianopia may be present. A lenticulostriate branch occlusion may cause a lacunar infarction with involvement of the internal capsule, producing a syndrome of pure motor hemiparesis. These syndromes are variable and depend on the presence of collaterals or whether brain edema is present.

Alexia with agraphia may occur with left-sided angular gyrus involvement. Gerstmann syndrome, which consists of finger agnosia, acalculia, right-left disorientation, and agraphia, may be seen with dominant-hemisphere parietal lesions. The aphasias with dominant-hemispheric infarctions may be of the Broca, Wernicke, conduction, transcortical, or global type, depending on the site and extent of involvement. *Anosognosia*, the denial of hemiparesis, is most commonly



Fig. 65.1 Nonenhanced axial computed tomographic scan of a 63-year-old man with left-sided weakness and abulia demonstrates a right anterior cerebral artery (ACA) territory infarction. More superior images showed the entire ACA distribution was infarcted.

associated with right hemispheric strokes. Nondominant infarction may cause hemi-inattention, tactile extinction, visual extinction, anosognosia, anosodiaphoria, apraxia, impaired prosody, and (rarely) acute confusion and agitated delirium. A contralateral homonymous hemianopia or contralateral inferior quadrantanopia can occur with infarctions in either hemisphere.

Syndromes of the Anterior Cerebral Artery and Related Blood Vessels

Anterior cerebral artery (ACA) territory infarctions are uncommon in isolation (Fig. 65.1). They occur in patients with vasospasm after subarachnoid hemorrhage caused by ACA or anterior communicating artery aneurysm. Excluding these causes, the percentage of acute cerebral infarcts that are in the ACA territory is less than 3%. The characteristics of ACA infarction vary according to the site of involvement and the extent of collateral blood flow. Contralateral weakness involving primarily the lower extremity and, to a lesser extent, the arm is characteristic of infarction in the territory of the hemispheric branches of the ACA. Other characteristics include abulia, akinetic mutism (with bilateral mesiofrontal damage), impaired memory or emotional disturbances, transcortical motor aphasia (with dominant hemispheric lesions), deviation of the head and eyes toward the lesion, paratonia (*gegenhalten*), discriminative and proprioceptive sensory loss (primarily in the lower extremity), and sphincter incontinence. An anterior disconnection syndrome with left arm apraxia due to involvement of the anterior corpus callosum can be seen. Pericallosal branch involvement can cause apraxia, agraphia, and tactile anomia of the left hand. Infarction of the basal branches of the ACA can cause memory disorders, anxiety, and agitation. Infarction in the territory of the medial lenticulostriate artery (artery of Heubner) causes more pronounced weakness

of the face and arm without sensory loss due to this artery's supply of portions of the anterior limb of the internal capsule.

The anterior choroidal artery syndrome is often characterized by hemiparesis caused by involvement of the posterior limb of the internal capsule, hemisensory loss caused by involvement of the posterolateral nucleus of the thalamus or thalamocortical fibers, and hemianopia secondary to involvement of the lateral geniculate body or the geniculocalcarine tract. The visual field defect with anterior choroidal artery syndrome infarcts is characterized by a homonymous defect in the superior and inferior visual fields that spares the horizontal meridian. In a small number of patients, left spatial hemineglect with right hemispheric infarctions, and a mild language disorder with left hemispheric infarctions, may occur. With bilateral infarctions in the anterior choroidal artery territory, there can be pseudobulbar mutism and a variety of other features including facial diplegia, hemisensory loss, lethargy, neglect, and affect changes.

Lacunar Syndromes

Ischemic strokes resulting from small-vessel or penetrating artery disease (lacunes) have unique clinical, radiological, and pathological features. Lacunar infarcts are small ischemic infarctions in the deep regions of the brain or brainstem that range in diameter from 0.5 to 15 mm. These infarctions result from occlusion of the penetrating arteries, chiefly the anterior choroidal, middle cerebral, posterior cerebral, and basilar arteries. Lacunar infarcts could also be the result of occlusion of penetrating arteries by atherosclerosis of the parent artery or by microembolism. Lacunes may be single or multiple, symptomatic or asymptomatic. At least 20 lacunar syndromes have been described. Lacunar syndromes are predictive of lacunar infarcts. The five best recognized syndromes are (1) pure motor hemiparesis, (2) pure sensory stroke, (3) sensorimotor stroke, (4) homolateral ataxia and crural paresis (ataxic hemiparesis), and (5) dysarthria-clumsy hand syndrome. Multiple lacunes may be associated with acquired cognitive decline. Headaches are uncommon in patients with lacunar infarcts.

Pure motor hemiparesis is often caused by an internal capsule, basis pontis, or corona radiata lacune and is characterized by a contralateral hemiparesis or hemiplegia involving the face, arm, and leg, accompanied by mild dysarthria, particularly at onset of stroke. There should be no aphasia, apraxia, or agnosia, and there are no sensory, visual, or other higher cortical disturbances. Pure sensory stroke is the least predictive syndrome of lacunar infarction but may be due to a lacune involving the ventroposterolateral nucleus of the thalamus. However, cortical infarcts of the postcentral gyrus may present with a similar syndrome. Pure sensory stroke is characterized by paresthesias, numbness, and a unilateral hemisensory deficit involving the face, arm, trunk, and leg. Sensory-motor stroke is often caused by a lacuna involving the internal capsule and thalamus or posterior limb of the internal capsule; large striatocapsular infarcts also can cause a similar syndrome. It is characterized by a contralateral motor deficit with a superimposed hemisensory deficit. Homolateral ataxia and crural paresis are often caused by a lacuna either in the posterior limb of the internal capsule or the basis pontis. It is characterized by weakness, predominantly in the contralateral lower extremity, and ipsilateral incoordination of the arm and leg. Dysarthria-clumsy hand syndrome is often caused by a lacuna involving the deep areas of the basis pontis and is characterized by supranuclear facial weakness, dysarthria, dysphagia, loss of fine motor control of the hand, and Babinski sign.

Vertebrobasilar System Syndromes

The areas of the cerebellum supplied by the posterior inferior cerebellar artery (PICA) are variable (see Chapter 21). There are several different patterns of PICA territory cerebellar infarctions. If the medial branch territory is affected, involving the vermis and vestibulocerebellum, the clinical findings include prominent vertigo, ataxia, and nystagmus. If the lateral cerebellar hemisphere is involved, patients can have vertigo, gait ataxia, limb dysmetria and ataxia, nausea, vomiting, conjugate or dysconjugate gaze palsies, miosis, and dysarthria. If the infarction is large, altered consciousness or confusion may occur as a result of cerebellar edema causing obstructive hydrocephalus or brainstem compression. Herniation downward through the foramen magnum or upward through the tentorial notch may occur leading to compression of vascular and parenchymal structures. Although a PICA occlusion can be the cause of Wallenberg (lateral medullary) syndrome, this syndrome is more often due to an intracranial vertebral artery occlusion.

The anterior inferior cerebellar artery (AICA) syndrome causes a ventral cerebellar infarction. The signs and symptoms include vertigo, nausea, vomiting, and nystagmus caused by involvement of the vestibular nuclei. There may be ipsilateral facial hypalgesia and thermoanesthesia and corneal hypesthesia because of involvement of the trigeminal spinal nucleus and tract. Ipsilateral deafness and facial paralysis occur with involvement of the lateral pontomedullary tegmentum. An ipsilateral Horner syndrome due to compromise of the descending oculosympathetic fibers is present. Contralateral trunk and extremity hypalgesia occurs, and involvement of the lateral spinothalamic tract causes thermoanesthesia. Finally, ipsilateral ataxia and asynergia follow involvement of the cerebellar peduncle and cerebellum.

Infarction in the territory of the superior cerebellar artery (SCA) produces a dorsal cerebellar syndrome (Fig. 65.2). Vertigo may be present, although it is less common with SCA infarcts than with the other cerebellar syndromes. Nystagmus is caused by involvement of the medial longitudinal fasciculus and the cerebellar pathways. An ipsilateral Horner syndrome due to involvement of the descending sympathetic tract may be present. Ipsilateral ataxia and asynergia and gait ataxia follow involvement of the superior cerebellar peduncle, brachium pontis, superior cerebellar hemisphere, and dentate nucleus. There is an intention tremor caused by involvement of the dentate nucleus and superior cerebellar peduncle. Choreiform dyskinesias may be present ipsilaterally. Contralaterally, there is hearing loss due to lateral lemniscus disruption and trunk and extremity hypalgesia and thermoanesthesia caused by spinothalamic tract involvement.

Weber syndrome is caused by infarction in the distribution of the penetrating branches of the posterior cerebral artery (PCA) affecting the cerebral peduncle, especially medially, with damage to the fascicle of cranial nerve III and the pyramidal fibers. The resultant clinical findings are contralateral hemiplegia of the face, arm, and leg secondary to corticospinal and corticobulbar tract involvement, and ipsilateral oculomotor paresis including a dilated pupil. A slight variation of this syndrome is the midbrain syndrome of Foville in which the supranuclear fibers for horizontal gaze are interrupted in the medial peduncle, causing conjugate gaze palsy to the opposite side. Benedikt syndrome is caused by a lesion affecting the mesencephalic tegmentum in its ventral portion, with involvement of the red nucleus, brachium conjunctivum, and fascicle of cranial nerve III. This syndrome is due to infarction in the distribution of the penetrating branches of the PCA to the midbrain. The clinical manifestations are ipsilateral oculomotor paresis, usually with pupillary dilation and

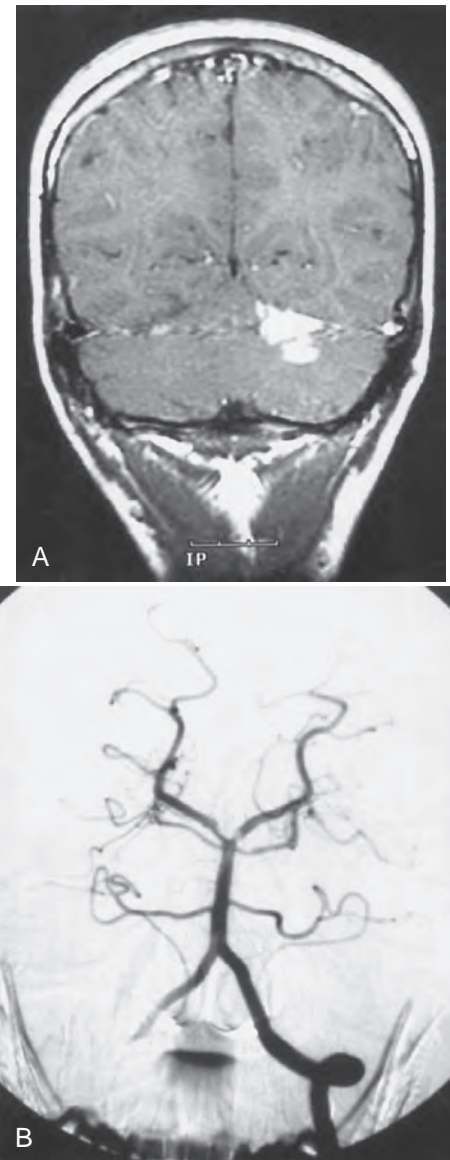


Fig. 65.2 A 15-year-old boy had vomiting, tinnitus, and unsteadiness. **A**, T1 coronal postgadolinium magnetic resonance imaging shows enhancing lesions in the superior aspect of the left cerebellar hemisphere consistent with superior cerebellar artery infarct. **B**, Anteroposterior view. Left vertebral artery injection shows a filling defect of the basilar apex also involving the proximal left superior cerebellar artery, consistent with thromboembolus.

contralateral involuntary movements including intention tremor, hemiathetosis, or hemichorea. Claude syndrome is caused by lesions that are more dorsally placed in the midbrain tegmentum than with Benedikt syndrome. There is injury to the dorsal red nucleus, which results in more prominent cerebellar signs without the involuntary movements. Oculomotor paresis occurs. Nothnagel syndrome is characterized by an ipsilateral oculomotor palsy with contralateral cerebellar ataxia. Infarction in the distribution of the penetrating branches of the PCA to the midbrain is the cause of this syndrome. Parinaud syndrome can result from infarctions in the midbrain territory of PCA penetrating branches. This syndrome is characterized by supranuclear paralysis of eye elevation, defective convergence, convergence-retraction nystagmus,

light-near dissociation, lid retraction, and skew deviation (see Chapter 21). Parinaud syndrome occurs more characteristically as a result of mass effect from midline mass lesions such as a pineal gland tumor.

Top of the basilar syndrome (see Chapter 21) is caused by infarction of the midbrain, thalamus, and portions of the temporal and occipital lobes. It is often due to embolic occlusion of the rostral basilar artery. Associated behavioral abnormalities include somnolence, peduncular hallucinosis, memory disturbances, or agitated delirium. Ocular findings include unilateral or bilateral paralysis of upward or downward gaze, impaired convergence, convergence-retraction nystagmus, abnormalities of ocular abduction due to pseudo-abducens palsy, Collier sign (which consists of elevation and retraction of the upper eyelids), skew deviation, and oscillatory eye movements. Visual defects that may be present include hemianopia, cortical blindness, and Balint syndrome. Pupillary abnormalities are variable and may be large or small, reactive or fixed. Motor deficits may also occur.

Although there are many named pontine syndromes, the most beneficial categorization is based on neuroanatomical divisions. Locked-in syndrome is the result of bilateral ventral pontine lesions that produce quadriplegia, aphonia, and impairment of horizontal eye movements in some patients. Wakefulness and normal sleep/wake cycles are maintained because the reticular formation is spared. The patient can move his or her eyes vertically and can blink, because the supranuclear ocular motor pathways lie more dorsally. In some patients with symptomatic basilar artery occlusive disease, there may be a herald hemiparesis that suggests a hemispheric lesion. However, within a few hours, there is progression to bilateral hemiplegia and cranial nerve findings associated with the locked-in syndrome. Pure motor hemiparesis and ataxia-hemiparesis caused by pontine lesions are discussed with the lacunar syndromes.

Occlusion of the AICA can lead to the lateral inferior pontine syndrome. Findings associated with this syndrome include ipsilateral facial paralysis, impaired facial sensation, paralysis of conjugate gaze to the side of the lesion, deafness, tinnitus, and ataxia. Contralateral to the lesion, there is hemibody impairment to pain and temperature that in some instances includes the face. There may be horizontal and vertical nystagmus as well as oscillopsia. The medial inferior pontine syndrome is caused by occlusion of a paramedian branch of the basilar artery. With this syndrome, there is ipsilateral paralysis of conjugate gaze to the side of the lesion, abducens palsy, nystagmus, and ataxia. Contralateral to the lesion, there is hemibody impairment of tactile and proprioceptive sensation and paralysis of the face, arm, and leg. An occlusion of the AICA may lead to the total unilateral inferior pontine syndrome, a combination of those symptoms and signs seen with the lateral and medial pontine syndromes.

The lateral pontomedullary syndrome can occur with occlusion of the vertebral artery. The manifestations are a combination of the medial and lateral inferior pontine syndromes.

Occlusion of the paramedian branch of the midbasilar artery can lead to ipsilateral impaired sensory and motor function of the trigeminal nerve with limb ataxia, characteristics of the lateral midpontine syndrome. Ischemia of the medial midpontine region is caused by occlusion of the paramedian branch of the midbasilar artery and can lead to ipsilateral limb ataxia. Contralateral to the lesion, eye deviation and paralysis of the face, arm, and leg occur. Although there are predominant motor symptoms, variable impaired touch and proprioception may also occur. The lateral superior pontine syndrome may occur with occlusion of the SCA and produces a characteristic syndrome of ipsilateral Horner syndrome, horizontal

nystagmus, paresis of conjugate gaze, occasional deafness, and severe ataxia of the limbs and gait. Contralateral to the lesion, there is hemibody impairment to pain and temperature, skew deviation, and impaired tactile, vibratory, and proprioceptive sensation in the leg greater than in the arm.

The lateral medullary syndrome (Wallenberg syndrome) is most often due to occlusion of the intracranial segment of the vertebral artery (eFig. 65.3). Less commonly, it is caused by occlusion of the PICA. This syndrome produces an ipsilateral Horner syndrome; loss of pain and temperature sensation in the face; weakness of the palate, pharynx, and vocal cords; and cerebellar ataxia. Contralateral to the lesion, there is hemibody loss of pain and temperature sensation. The medial medullary (Dejerine) syndrome is less common and may be caused by occlusion of the distal vertebral artery, a branch of the vertebral artery, or the lower basilar artery. Vertebral artery dissection, dolichoectasia of the vertebrobasilar system, and embolism are less common causes of the medial medullary syndrome. The findings with this syndrome include an ipsilateral lower motor neuron paralysis of the tongue and contralateral paralysis of the arm and leg. The face is often spared. In addition, there is contralateral hemibody loss of tactile, vibratory, and position sense. Occlusion of the intracranial vertebral artery can lead to a total unilateral medullary syndrome (of Babinski-Nageotte) or a combination of the medial and lateral medullary syndromes.

Posterior Cerebral Artery Syndromes

The manifestations with PCA territory infarctions are variable depending on the site of the occlusion and the availability of collateral blood flow. Occlusion of the precommunal P1 segment causes midbrain, thalamic, and hemispheric infarction. Occlusion of the PCA in the proximal ambient cisternal segment before branching in the thalamogeniculate pedicle causes lateral thalamic and hemispheric symptoms. Occlusions also may affect a single PCA branch, primarily the calcarine artery, or cause a large hemispheric infarction of the PCA territory. Unilateral infarctions in the distribution of the hemispheric branches of the PCA may produce a contralateral homonymous hemianopia caused by infarction of the striate cortex, the optic radiations, or the lateral geniculate body. There is partial or complete macular sparing if the infarction does not reach the occipital pole. The visual field defect may be limited to a quadrantanopia. A superior quadrantanopia is due to infarction of the striate cortex inferior to the calcarine fissure or the inferior optic radiations in the temporo-occipital lobes. An inferior quadrantanopia is the result of an infarction of the striate cortex superior to the calcarine fissure or the superior optic radiations in the parieto-occipital lobes.

More complex visual changes may occur, including formed or unformed visual hallucinations, visual and color agnosias, or prosopagnosia. Finally, some alteration of sensation with PCA hemispheric infarctions occurs, including paresthesias or altered position, pain, and temperature sensations. Infarction in the distribution of the callosal branches of the PCA involving the left occipital region and the splenium of the corpus callosum produces alexia without agraphia (Fig. 65.4). In this syndrome, patients can write, speak, and spell normally but are unable to read words and sentences. The ability to name letters and numbers may be intact, but there can be inability to name colors, objects, and photographs. Right-hemispheric PCA territory infarctions may cause contralateral visual-field neglect. Amnesia may be present with PCA infarctions that involve the left medial temporal lobe or when there are bilateral mesiotemporal infarctions. In addition, an agitated delirium may occur with unilateral or bilateral



eFig. 65.3 A 74-year-old man had sudden onset of vertigo, vomiting, and gait unsteadiness. T2-weighted axial magnetic resonance imaging of the brain demonstrates an infarct in the posterolateral side of the medulla and a small cerebellar infarct in the distribution of the left posterior inferior cerebellar artery. There is poor flow void seen in the left vertebral artery.

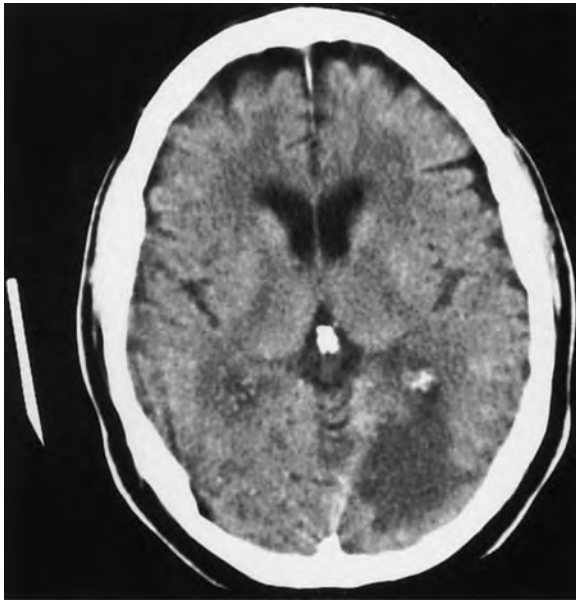


Fig. 65.4 A 77-year-old man had alexia without agraphia, right homonymous hemianopia, and anterograde amnesia. Nonenhanced axial cranial computed tomography demonstrates an area of decreased parenchymal attenuation in the left occipitoparietal region.

penetrating mesiotemporal infarctions. Large infarctions of the left posterior temporal artery territory may produce an anomic or transcortical sensory aphasia.

Infarctions in the distribution of the penetrating branches of the PCA to the thalamus can cause aphasia (if the left pulvinar is involved), akinetic mutism, global amnesia, and Dejerine-Roussy syndrome. In the latter syndrome, the patient has contralateral sensory loss to all modalities, severe dysesthesias on the involved side (thalamic pain), vasomotor disturbances, transient contralateral hemiparesis, and choreoathetoid or ballistic movements. A number of syndromes that can result from infarctions in the distribution of the penetrating branches of the PCA to the midbrain were previously discussed with the midbrain syndromes.

Bilateral infarctions in the distribution of the hemispheric branches of the PCAs may cause bilateral homonymous hemianopias. Bilateral occipital or occipitoparietal infarctions can cause cortical blindness, often with denial or unawareness of blindness (Anton syndrome). Balint syndrome, seen with bilateral occipital or parieto-occipital infarctions, consists of optic ataxia, optic apraxia (paralysis of voluntary fixation), with inability to look to the peripheral field and disturbance of visual attention, and simultanagnosia (see Chapter 93).

Syndromes of Thalamic Infarction

The main thalamic blood supply comes from the posterior communicating arteries and the perimesencephalic segment of the PCA. Thalamic infarctions typically involve one of four major vascular regions: posterolateral, anterior, paramedian, and dorsal. Posterolateral thalamic infarctions result from occlusion of the thalamogeniculate branches arising from the P2 segment of the PCA. Three common clinical syndromes may occur: pure sensory stroke, sensorimotor stroke, and the thalamic syndrome of Dejerine-Roussy. Anterior thalamic infarction results from occlusion of the polar or tuberothalamic artery. Bilateral thalamic infarction may occur with an anatomic variant whereby the rostral mesencephalon and para-

median thalami receive flow from a single thalamic perforating artery known as the artery of Percheron (see eFig. 65.5), which is typically present contralateral to an absent P1 segment of a posterior cerebral artery. An absent or atretic P1 segment may occur as a normal variant when the PCA has a persistent fetal pattern arising directly from the intracranial internal carotid artery. The main clinical manifestations of thalamic infarction consist of neuropsychological disturbances, emotional-facial paresis, occasional hemiparesis, and visual-field deficits. Left-sided infarcts are associated with dysphasia, whereas neglect is seen primarily in patients with right-sided lesions. Paramedian thalamic infarctions result from occlusion of the paramedian, thalamic, and subthalamic arteries. The main clinical manifestations include the classic triad of decreased level of consciousness, memory loss, and vertical-gaze abnormalities. Dorsal thalamic infarctions result from occlusion of the posterior choroidal arteries. These infarctions are characterized by the presence of homonymous quadrantanopia or horizontal sectoranopias. Involvement of the pulvinar may account for thalamic aphasia.

Watershed Ischemic Syndromes

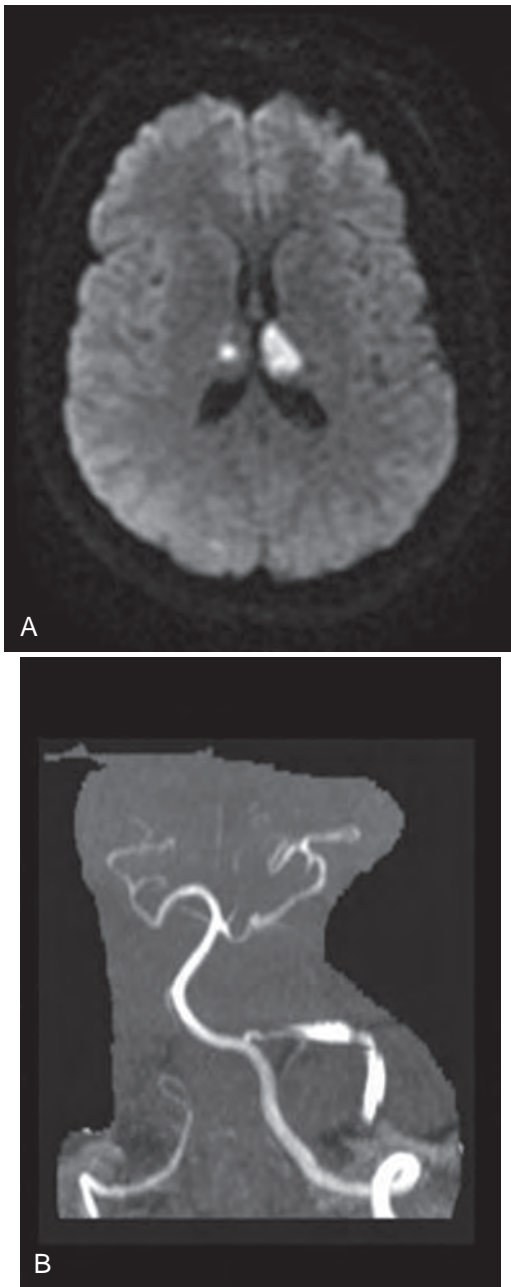
Watershed infarcts occur in the border zone between adjacent arterial perfusion beds. During or after cardiac surgery or after an episode of sustained and severe arterial hypotension that can happen after cardiac arrest, prolonged hypoxemia, or bilateral severe carotid artery disease, ischemia may occur in the border zones between the major circulations. Watershed infarctions may be unilateral when there is only a relative degree of hemodynamic failure in patients with underlying unilateral severe arterial stenosis or occlusion. Border zone infarcts also may be caused by microembolism or hyperviscosity states.

Ischemia in the border zone or junctional territory of the ACA, MCA, and PCA may result in bilateral parieto-occipital infarcts. There can be a variety of visual manifestations, including bilateral lower altitudinal-field defects, optic ataxia, cortical blindness, and difficulty in judging size, distance, and movement. Ischemia between the territories of the ACA and MCA bilaterally may result in bi-brachial cortical sensorimotor impairment ("person in a barrel") and impaired saccadic eye movements caused by compromise of the frontal eye fields. Ischemia in the border zone between the MCA and PCA may cause bilateral parieto-temporal infarctions. Initially there is cortical blindness that may improve, but defects such as dyslexia, dyscalculia, dysgraphia, and memory defects for verbal and nonverbal material may persist.

Watershed infarcts are also recognized between the territorial supply of the PICA, AICA, and SCA. Watershed infarctions may also involve the internal border zone in the centrum semiovale adjacent to and slightly above the body of the lateral ventricles.

DIAGNOSIS AND TREATMENT OF THREATENED ISCHEMIC STROKE

An ischemic stroke develops when there is interrupted cerebral blood flow to an area of the brain. Ischemic strokes account for approximately 80% to 88% of all strokes. Ischemic strokes may result from (1) large-artery atherosclerotic disease resulting in stenosis or occlusion, (2) small-vessel or penetrating artery disease (lacunes), (3) cardiogenic or artery-to-artery embolism, (4) nonatherosclerotic vasculopathies, (5) hypercoagulable disorders, and (6) infarcts of undetermined causes. The most recognized mechanistic classification is the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification



eFig. 65.5 A, Diffusion-weighted magnetic resonance imaging sequence showing bilateral thalamic infarcts in a 42-year-old woman. **B**, Magnetic resonance angiogram of the patient in **A** showing normal origin of the right posterior cerebral artery and absence of P1 segment of the left posterior cerebral artery in the setting of a left posterior cerebral artery with persistent fetal origin.

(Madden et al., 1995). However, a rigid classification of ischemic stroke subtypes is difficult to establish because of the frequent occurrence of mixed syndromes.

LARGE-ARTERY ATHEROTHROMBOTIC INFARCTIONS

Large-artery atherothrombotic infarctions almost always occur in patients who already have significant risk factors for cerebrovascular atherosclerosis (see Table 65.1). Atherothrombosis is multifactorial, comorbidities frequently overlap, and risk factors are often additive. For example, arterial hypertension is often associated with hyperlipidemia, hyperglycemia, elevated fibrinogen levels, excessive weight, and left ventricular hypertrophy on ECG. A resting ankle-brachial index of less than 0.90 is indicative of generalized atherosclerosis. Persons with a stroke are at high risk for development of other vascular complications. After a stroke, there is a 25% chance of a fatal thrombotic event in 3 years. Many of these deaths are due to MI. The mechanism of large-artery atherothrombotic infarction is often artery-to-artery embolization or thrombosis in the setting of pre-existing arterial stenosis. Arteriogenic embolism from ulcerated carotid artery atherosclerotic plaques is a common cause of cerebral infarction (Fig. 65.6). In situ thrombosis occurs in the proximal carotid artery, distal vertebral artery, and lower or middle basilar artery (Fig. 65.7). Atherosclerotic involvement of the intracranial portion of the vertebrobasilar system frequently occurs in tandem and is the common pathological mechanism associated with the

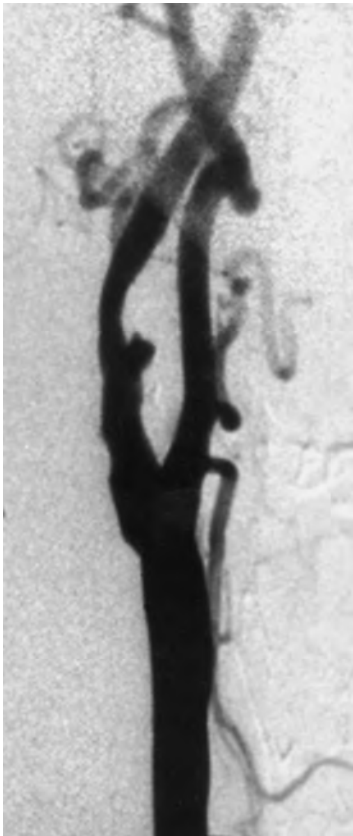


Fig. 65.6 Right common carotid angiogram shows 17% right internal carotid artery stenosis (North American Symptomatic Carotid Endarterectomy Trial criteria) just superior to a large carotid ulceration. (Courtesy Vincent Mathews, MD.)

syndrome of vertebrobasilar territory infarction; this may also arise in association with hypercoagulable states. Hypoperfusion secondary to hemodynamic alterations also may trigger these events. The pathogenesis of stroke due to intracranial arterial stenosis may be similar to stroke due to extracranial arterial disease (Qureshi and Caplan, 2014).

In patients with risk factors for atherosclerosis, the cholesterol-rich minimally raised fatty streak may progress to a fibrous plaque that can evolve into a complicated plaque with intraplaque hemorrhage, extensive necrosis, calcification, and subsequent thrombosis (Fig. 65.8). The infiltration of the fibrous cap by inflammatory cells may contribute to the rupture of the atherosclerotic carotid artery plaque. Atherosclerosis is often segmental and asymmetrical, and earlier lesions tend to occur in areas of low shear stress, such as the outer aspect of the carotid artery bulb. Atherosclerosis primarily affects the larger extracranial and intracranial vessels, particularly the bifurcation of the common carotid artery and proximal internal carotid artery, the carotid siphon, MCA

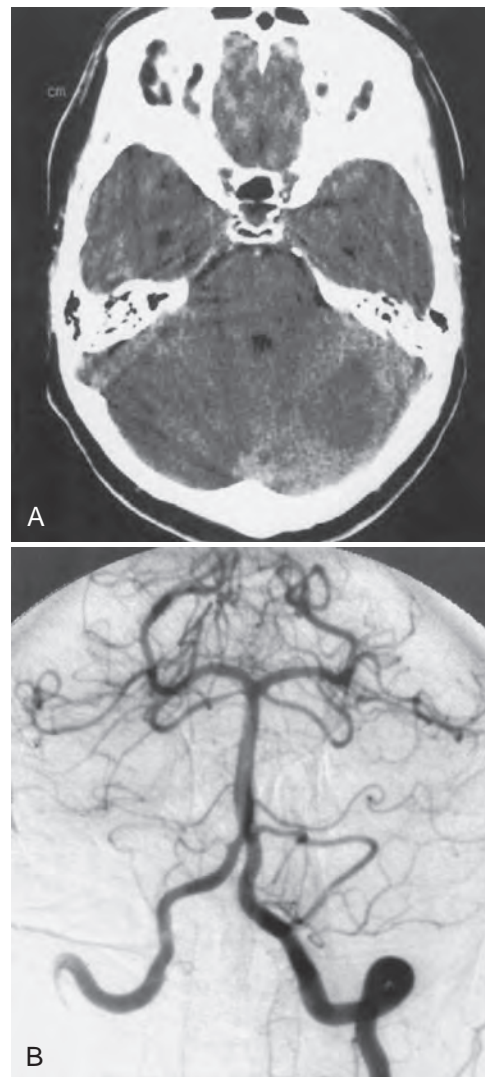


Fig. 65.7 **A**, Nonenhanced axial computed tomographic scan shows bilateral cerebellar and pontine infarcts. **B**, Anteroposterior view of vertebrobasilar angiogram shows a large filling defect on the basilar artery, consistent with partial thrombosis. (Courtesy Vincent Mathews, MD.)



Fig. 65.8 Left carotid angiogram (lateral view) shows severe stenosis (open arrow) of origin of the left internal carotid artery, with an intraluminal thrombus (arrow). The artery was occluded in other images. (Courtesy Vincent Mathews, MD.)

stem, origin of the vertebral arteries (V1), intracranial segment of the vertebral arteries (V4), and basilar artery. The distribution of cerebral atherosclerosis may be different in certain ethnic groups. Stenosis of major intracranial arteries is more prevalent among blacks and Asians than in whites, but this may also reflect ascertainment biases.

SMALL-VESSEL OR PENETRATING ARTERY DISEASE

Lacunae usually occur in patients with long-standing arterial hypertension, current cigarette smoking, and DM. The most frequent sites of involvement are the putamen, basis pontis, thalamus, posterior limb of the internal capsule, and caudate nucleus. Multiple lacunae are strongly associated with arterial hypertension and DM. Available evidence suggests that structural changes of the cerebral vasculature caused by arterial hypertension are characterized by fibrinoid angiopathy, lipohyalinosis, and microaneurysm formation. Accelerated hypertensive arteriolar damage of the small penetrating arteries is operative in a large number of patients with lacunar infarction. However, microatheroma of the ostium of a penetrating artery, arterial or cardiac embolism, or changes in hemorheology can be pathophysiologically operative in the remainder of cases. Microatheroma are associated with the majority of lacunae greater than 50 μm . The mere association of a lacunar syndrome in a patient with arterial hypertension and diabetes is insufficient for a diagnosis of lacunar infarct, and other causes of ischemic stroke must be excluded. In particular, the presence of sensorimotor stroke, limb weakness and sudden onset in a patient with atrial fibrillation, and large striatocapsular infarctions should be distinguished from lacunar infarcts, because they frequently have potential cardioembolic sources or coexistent severe carotid or MCA stenosis, and they often present with signs and symptoms of cortical dysfunction (Arboix et al., 2010). Control of hypertension, intensive statin therapy, and judicious use of platelet

antiaggregants are essential in the management of patients with lacunar infarcts.

CARDIOGENIC EMBOLISM

Cerebrovascular events are a serious complication for a diverse group of cardiac disorders. Cardioembolic strokes are associated with substantial morbidity and mortality. Embolism of cardiac origin accounts for approximately 15% to 20% of all ischemic strokes. These cardiac emboli may be composed of platelet, fibrin, platelet-fibrin, calcium, microorganisms, or neoplastic fragments. The most common substrate for cerebral embolism in older individuals is atrial fibrillation, accounting for half to two-thirds of emboli of cardiac origin. Other cardiac conditions with high embolic potential include acute MI, infective endocarditis, rheumatic mitral stenosis, mechanical prosthetic heart valves, dilated cardiomyopathy, and cardiac tumors. Low or uncertain embolic risk disorders include mitral valve prolapse, mitral annulus calcification, aortic valve calcification, calcific aortic stenosis, remote MI, left ventricular aneurysm, hypertrophic cardiomyopathy, patent foramen ovale (PFO), atrial septal aneurysm (ASA), atrial flutter, valvular strands, and a Chiari network.

Congenital heart disease is the most common cardiac disorder causing ischemic stroke in children. With the increased survival of many children with congenital heart disease, strokes are being seen with increased frequency. Children with congenital heart disease and a low hemoglobin concentration are at special risk for arterial strokes; those with a high hematocrit are more likely to experience cerebral venous thrombosis. Emboli from cardiac sources may be silent or cause severe neurological deficit or death. Although most types of heart disease may produce cerebral embolism, certain cardiac disorders are more likely to be associated with emboli (Box 65.2).

Cardioembolic cerebral infarcts are often large, multiple, bilateral, and wedge shaped. Sudden unheralded focal neurological deficits that are worse at onset are often presenting manifestations of a cardioembolic infarction. Any vascular territory may be affected. Ischemic strokes with a potential cardiac source are more often associated with Wernicke aphasia, homonymous hemianopia without hemiparesis or hemisensory disturbances, and ideomotor apraxia. Other features suggestive of a potential cardiac source of embolism include inferior division of the MCA compromise; involvement of multiple vascular territories; or a hemorrhagic component of the infarction. Reliable clinical determination of a cardioembolic source of stroke may be hampered by a variety of problems. Identification of a potential embolic cardiac source is not by itself sufficient to diagnose a brain infarct as cardioembolic because (1) many cardiac problems may coexist with cerebrovascular atherosclerosis, (2) cardiac arrhythmias may occur after arrhythmogenic lesions such as parietoinsular and brainstem infarcts, (3) brain imaging differentiation between cardioembolic and atherosclerotic causes of cerebral infarction is not always reliable, and (4) cardiac changes detected by echocardiography are prevalent in control populations.

An embolic stroke occurs in approximately 1% of hospitalized patients with acute MI. Left ventricular thrombi are commonly associated with recent anterior wall transmural MI. Echocardiographic studies have demonstrated that approximately one-third to one-half of acute anterior MIs but less than 4% of acute inferior MIs develop left ventricular thrombi. Almost all episodes of embolism occur within 3 months following acute MI, with 85% of emboli developing in the first 4 weeks. A decreased ejection fraction is an independent predictor of stroke following MI. Although the prevalence of left ventricular thrombi in individuals with left ventricular

BOX 65.2 Sources of Cardioembolism

Acute myocardial infarction
 Left ventricular aneurysm
 Dilated cardiomyopathy
 Cardiac arrhythmias
 Atrial fibrillation
 Sick sinus syndrome
 Valvular heart disease
 Rheumatic mitral valve disease
 Calcific aortic stenosis
 Mitral annulus calcification
 Mitral valve prolapse
 Infective endocarditis
 Nonbacterial thrombotic endocarditis
 Prosthetic heart valves
 Filamentous strands of the mitral valve
 Giant Lambl excrescences
 Aneurysms of the sinus of Valsalva
 Intracardiac tumors (atrial myxoma, rhabdomyoma, papillary fibroelastoma)
 Intracardiac defects with paradoxical embolism
 Patent foramen ovale
 Atrial septal aneurysm
 Atrial septal defect
 Cyanotic congenital heart disease
 Fontan procedure or its modifications (cavopulmonary anastomosis)
 Mitochondrial encephalomyopathies (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes; myoclonic epilepsy and ragged-red fibers; Kearns-Sayre syndrome)
 Coronary artery bypass grafting
 VVI pacing
 Heart transplantation
 Artificial hearts
 Cardioversion for atrial fibrillation
 Balloon angioplasty
 Ventricular support devices
 Extracorporeal membrane oxygenator

aneurysms is high, the frequency of systemic embolism is low. Dilated or congestive cardiomyopathy may result from arterial hypertension or a variety of inflammatory, infectious, immune, metabolic, toxic, and neuromuscular disorders. The global impairment of ventricular performance predisposes to stasis and thrombus formation. Patients commonly have signs of impaired left ventricular systolic function, and less than half have diastolic heart failure. Occasionally, patients have concomitant atrial fibrillation. A cerebral embolism may be the presenting manifestation of heart failure. Embolism occurs in approximately 18% of patients with dilated cardiomyopathy not receiving anticoagulants. Patients with idiopathic hypertrophic subaortic stenosis may also present with stroke. Thromboembolism is not uncommon in patients with congestive heart failure. Mitochondrial disorders (see Chapter 93) are seldom associated with dilated cardiomyopathies, but cerebral infarction is a complication of mitochondrial encephalomyopathies (MELAS, myoclonic epilepsy and ragged-red fibers, and Kearns-Sayre syndrome). Stroke in Kearns-Sayre syndrome is likely secondary to embolism. Apical aneurysms also complicate Chagas cardiomyopathy, with resultant cerebral embolism.

Most cases of mitral stenosis are due to rheumatic heart disease. Systemic emboli occur in 9% to 14% of patients with

mitral stenosis, with 60% to 75% having cardioembolic cerebral ischemia. Systemic embolism may be the first symptom of mitral stenosis, particularly if it is associated with atrial fibrillation. Aortic valve calcification with or without stenosis is not a major risk factor for stroke, but cases have been described. Cerebral embolism is a rare but described occurrence in patients with bicuspid aortic valves. Individuals with mitral annular calcification (MAC) have a twofold risk for stroke compared with those without MAC, but stroke rates are low. Mitral valve prolapse affects 3% to 4% of adults and when uncomplicated does not seem to increase their risk for stroke. Neurological ischemic events appear to occur more commonly among men older than 50 years who have auscultatory findings of a systolic murmur and thick mitral valve leaflets on echocardiography. Thromboembolic phenomena complicating infective endocarditis may be systemic (left-sided endocarditis) or pulmonary (right-sided endocarditis). Vegetations are detected by transthoracic echocardiography in the majority of patients with infective endocarditis and are associated with an increased risk for embolism. Transesophageal echocardiography is the gold standard, however, with detection rates of better than 90%. Systemic emboli may occur in nearly half of patients with nonbacterial thrombotic endocarditis, a condition characterized by the presence of multiple small, sterile thrombotic vegetations most frequently involving the mitral and aortic valves. The risk for thromboembolism is higher with mechanical prosthetic heart valves than with biological prosthetic heart valves. Thromboemboli are more common with prosthetic heart valves in the mitral position than with prosthetic heart valves in the aortic position. The rate of systemic embolism in patients with mechanical heart valves receiving anticoagulant therapy is 4% per year in the mitral position and 2% per year in the aortic position. Filamentous strands attached to the mitral valve appear to represent a risk for cerebral embolism, particularly in young patients, but the risk for recurrent cerebral ischemia is incompletely understood. The association between cerebral embolism and giant Lambl excrescences or aneurysms of the sinus of Valsalva is low.

Atrial fibrillation is the most common cardiac arrhythmia requiring hospitalization in the United States. The incidence of thromboembolism in patients with atrial fibrillation is 4% to 7.5% per year. Patients with NVAf, the leading source of cardioembolic infarctions in older adults, have a five- to sixfold increase in stroke incidence, with a cumulative risk of 35% over a lifetime. Patients with rheumatic atrial fibrillation have a 17-fold increase in stroke incidence. However, individuals younger than age 65 with lone atrial fibrillation have a low embolic potential particularly when heart failure, hypertension, DM, and previous history of stroke or TIA are absent. Stroke patients with atrial fibrillation are also at high risk for death during the acute phase of stroke and during the subsequent year after stroke. A dramatic increase in the prevalence of atrial fibrillation occurs with age, from 0.2 cases per 1000 patients aged 30 to 39 years to 39 cases per 1000 patients aged 80 to 89 years. The proportion of strokes caused by atrial fibrillation also steadily increases from 6.7% of all strokes in patients aged 50 to 59 years to 36.2% in those aged 80 to 89 years. The risk for embolism is increased among patients with atrial fibrillation and hyperthyroidism, who also have an increased sensitivity to warfarin.

Cerebral and systemic embolism also may occur in the setting of the sick sinus syndrome. Patients at greatest risk for embolization have bradytachyarrhythmias; left atrial spontaneous echocardiographic contrast and decreased atrial ejection force increase stroke risk. Patients with sick sinus syndrome may experience cerebral ischemia or systemic embolism even after pacemaker insertion. Ventricular-inhibited (VVI) pacing

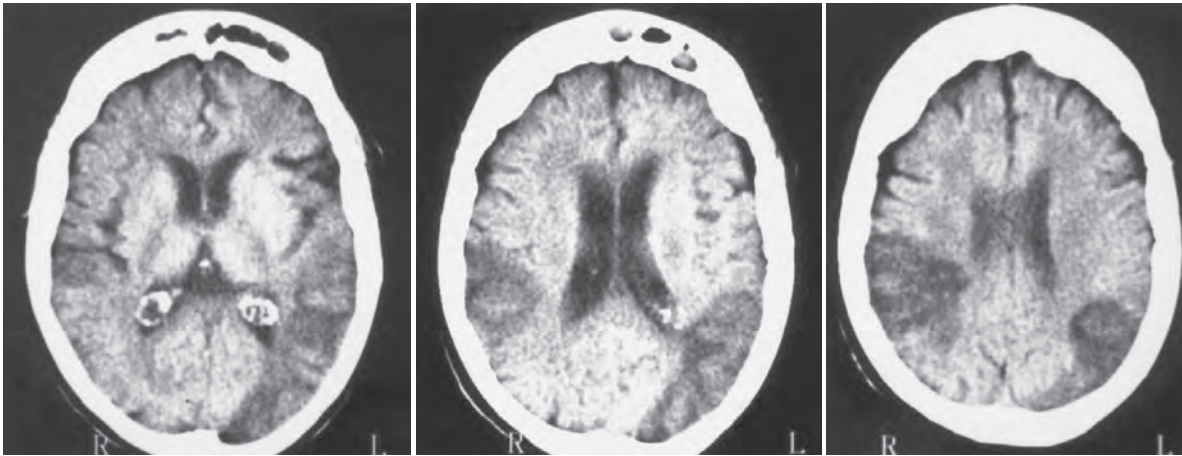


Fig. 65.9 An 80-year-old woman remained unresponsive, with left-sided hemiplegia and right-sided hemiparesis after coronary artery bypass grafting and aortic valve replacement. Nonenhanced axial computed tomography demonstrates large left temporo-parieto-occipital and right frontoparietal infarctions.

is associated with a higher risk for embolic complications than atrial or dual-chamber pacing. The risk for thromboembolism is also higher among patients in chronic atrial flutter.

Atrial myxomas are rare cardiac tumors complicated by postural syncope and systemic and embolic manifestations. Atrial myxomas can result in stroke due to embolism of myxomatous material or thrombus. Embolic complications are a presenting symptom in one-third of patients with atrial myxoma. Recurrent emboli before surgery are common. Peripheral and multiple cerebral arterial aneurysms also have been diagnosed years following the initial embolic manifestations from atrial myxoma. Treatment of atrial myxomas consists of prompt surgical resection of the cardiac mass. Cardiac rhabdomyomas are associated closely with tuberous sclerosis; systemic embolism is unusual. Mitral valve papillary fibroelastoma, an uncommon valvular tumor, is complicated rarely by stroke.

A paradoxical embolism caused by a right-to-left shunt through a PFO or ASA can be responsible for stroke and other ischemic cerebral events. A PFO provides opportunity for right-to-left shunting during transient increases in the right atrial pressure. A PFO is present in 35% of subjects without stroke between the ages of 1 and 29 years, in 25% of people between the ages of 30 and 79 years, and in 20% between the ages of 80 and 99 years. A PFO is more common in patients with stroke than in matched controls. Patients with no identifiable cause for ischemic stroke (cryptogenic stroke) and PFO may have a larger PFO with more extensive right-to-left shunting than patients with stroke of determined cause. Platelet antiaggregants, oral anticoagulants, transcatheter closure of the PFO, or surgical closure of the PFO have been recommended. However, the benefit of PFO closure over medical strategies for recurrent stroke prevention has not been established (NMT Medical, 2010). Cerebrovascular complications of percutaneous PFO closure can include air embolism or thromboembolism, atrial fibrillation, infective endocarditis, or delayed cardioembolic stroke due to thrombus formation around the device. A study found no difference in the time to primary endpoints between aspirin and warfarin (mean INR = 2.04) (Homma et al., 2002). ASA also might be a source of cerebral emboli. Only one study has reported that the coexistence of PFO and ASA increases the risk for embolic stroke (Messe et al., 2004). PFO and ASA also have been associated with mitral valve prolapse. Strokes are sometimes severe, but recurrences are uncommon in the context of PFO-related

stroke. Pulmonary arteriovenous malformations can also be a source of paradoxical embolism causing cerebral ischemia and occur in 15% to 20% of patients with Rendu-Osler-Weber syndrome.

Spontaneous echocardiographic contrast is associated with elevated fibrinogen levels and plasma viscosity and is a potential risk factor for cardioembolic stroke. Spontaneous echocardiographic contrast is highly associated with previous stroke or peripheral embolism in patients with atrial fibrillation or mitral stenosis and increased left atrial size. The risk for cerebrovascular events is increased in adults with cyanotic congenital heart disease in the presence of arterial hypertension, atrial fibrillation, history of phlebotomy, and particularly with microcytosis.

The preponderance of posterior circulation ischemia following cardiac catheterization is unexplained. Stroke occurs after coronary artery bypass grafting with a frequency ranging between 1% and 5% (Fig. 65.9). Two-thirds of strokes occur by the second postoperative day and predominantly involve the cerebral hemispheres; brainstem/cerebellar infarcts and lacunar strokes are less common. The cause of postoperative stroke is multifactorial; hypoperfusion, ventricular thrombus, and emboli are probable causal factors, although embolic causes are the most likely mechanisms. Clamp manipulation during coronary artery bypass surgery also may favor the release of aortic atheromatous debris. Epiaortic ultrasound studies demonstrate an increased stroke rate associated with an increased severity of aortic atherosclerosis. Strokes following coronary artery bypass grafting rarely relate to carotid artery stenosis. Carotid artery occlusion, but not carotid artery stenosis, increases the risk for stroke following coronary artery bypass grafting. Thromboembolic phenomena can complicate cardiac surgery using cardiopulmonary bypass with deep hypothermia and cardiac arrest. Stroke is a potential complication of cardioversion for atrial fibrillation. Cerebral embolism may also complicate valvuloplasty; the risk is greater for aortic rather than mitral valvuloplasty. Strokes may follow heart transplantation, the use of ventricular support systems and artificial hearts, and the use of the extracorporeal membrane oxygenator. Stroke following inadvertent placement of left-sided heart pacemaker leads is an unusual complication. Ischemic myelopathy is a rare complication of the intra-aortic balloon pump. Aortic dissection or hematoma may lead to an occlusion of a major radicular branch or local occlusion of the artery of Adamkiewicz (see Chapter 68).

BOX 65.3 Selected Nonatherosclerotic Vasculopathies

Cervicocephalic arterial dissections
 Traumatic cerebrovascular disease
 Radiation-induced vasculopathy
 Moyamoya disease
 Fibromuscular dysplasia
 Vasculitis
 Migrainous infarction

NONATHEROSCLEROTIC VASCULOPATHIES

Although the majority of arterial disorders leading to stroke are caused by atherosclerosis, several nonatherosclerotic vasculopathies can be responsible for a minority of ischemic strokes. These vasculopathies include cervicocephalic arterial dissections, traumatic cerebrovascular disease, radiation vasculopathy, moyamoya, fibromuscular dysplasia (FMD), and cerebral vasculitis (Boxes 65.3 and 65.4). Together, these uncommon conditions represent 5% of all ischemic strokes. They are relatively more common in children and young adults.

Dissections

Cervicocephalic arterial dissections are one of the most frequent nonatherosclerotic vasculopathies causing ischemic stroke in young adults. A dissection is produced by subintimal penetration of blood with subsequent longitudinal extension of the intramural hematoma between vascular layers. Most dissections involve the extracranial segment of the internal carotid artery or extracranial vertebral arteries. Intracranial carotid and vertebrobasilar dissections are less common; intracranial dissections are usually subintimal and may follow trivial trauma, closed head trauma, basilar skull fracture, or penetrating injuries. The recurrence rate of extracranial cervicocephalic arterial dissections is approximately 1% per year. The risk for recurrent dissections is increased in younger patients, those with a history of FMD, and in patients with family history of arterial dissections.

Cervicocephalic arterial dissections have been reported after blunt or penetrating trauma and also are associated with FMD, Marfan syndrome, Turner syndrome (Muscat et al., 2001), Williams syndrome (Vanacker and Thijs, 2009), Ehlers-Danlos syndrome type IV, pseudoxanthoma elasticum, coarctation of the aorta, Menkes disease, α_1 -antitrypsin deficiency, cystic medial degeneration, reticular fiber deficiency, accumulation of mucopolysaccharides, hereditary hemochromatosis (Gallerini et al., 2006), osteogenesis imperfect type I, adult polycystic kidney disease, elevated arterial elastase content, lentiginosis, atherosclerosis, extreme vessel tortuosity, moyamoya syndrome, hyperhomocysteinemia (Arauz et al., 2007), the 677TT genotype of the 5,10-methylenetetrahydrofolate reductase gene (MTHFR 677TT), pharyngeal infections, sympathomimetic drug abuse, luetic arteritis, and styloid process length (Raser et al., 2011). Most cervicocephalic arterial dissections occur either spontaneously or in relation to minor trauma (Debette and Leys, 2009).

Dissection of the cervicocephalic vessels may cause transient retinal, hemispheric, or posterior fossa ischemia; Horner syndrome; hemicranial or neck pain; cranial nerve palsies; cerebral infarction; or subarachnoid hemorrhage when the dissection involves an intracranial vessel due to the absence of an external elastic lamina beyond penetration through the dura. Ischemic symptoms result from arterial occlusion or secondary embolization. In addition to a postganglionic Horner syndrome, neuro-ophthalmological manifestations of

BOX 65.4 Classification of Cerebral Vasculitides

Infectious vasculitis:
 Bacterial, fungal, parasitic
 Spirochetal (syphilis, Lyme disease)
 Viral, rickettsial, mycobacterial
 Cysticercosis, free-living amebae

Necrotizing vasculitides:
 Classic polyarteritis nodosa
 Granulomatosis with polyangiitis
 Allergic angiitis and granulomatosis (Churg–Strauss)
 Necrotizing systemic vasculitis-overlap syndrome
 Lymphomatoid granulomatosis

Vasculitis associated with collagen vascular disease:
 Systemic lupus erythematosus
 Rheumatoid arthritis
 Scleroderma
 Sjögren syndrome

Vasculitis associated with other systemic diseases:
 Behçet disease
 Ulcerative colitis
 Sarcoidosis
 Relapsing polychondritis
 Kohlmeier–Degos disease (malignant atrophic papulosis)

Giant cell arteritides:
 Takayasu arteritis
 Temporal (cranial) arteritis

Hypersensitivity vasculitides:
 Henoch–Schönlein purpura
 Drug-induced vasculitides
 Chemical vasculitides
 Essential mixed cryoglobulinemia

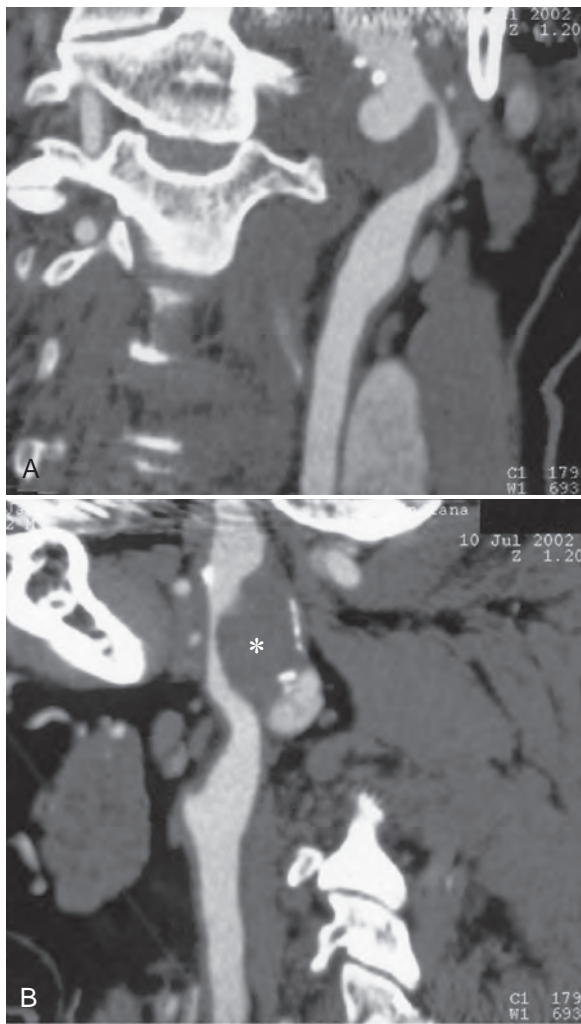
Miscellaneous:
 Vasculitis associated with neoplasia
 Vasculitis associated with radiation
 Cogan syndrome
 Dermatomyositis polymyositis
 X-linked lymphoproliferative syndrome
 Thromboangiitis obliterans
 Kawasaki syndrome
 Primary central nervous system vasculitis
 Amyloid-beta related angiitis

From Biller, J., Sparks, L.H., 1993. *Diagnosis and management of cerebral vasculitis*. In: Adams Jr., H.P. (Ed.), *Handbook of Cerebrovascular Diseases*. Marcel Dekker, New York, p. 150.

internal carotid artery dissections may also include central retinal artery occlusion, ophthalmic artery occlusion, ischemic optic neuropathy, homonymous hemianopia, and ocular motor nerve palsies (cranial nerve [CN] III, IV, and VI). In addition to a first-order neuron Horner syndrome, other neuro-ophthalmological manifestations of vertebrobasilar dissections include diplopia, nystagmus, oscillopsia, ocular misalignment, skew deviation, ocular motor nerve palsies (CN III, IV, and VI), lateral gaze palsy, internuclear ophthalmoplegia, and homonymous visual-field defects.

Cervicocephalic arterial dissections should be considered in the differential diagnosis of ischemic stroke in any young adult, particularly when traditional risk factors are absent. Diagnosis is based on arteriographic findings, although high-resolution MRI with T1 fat suppression sequences and magnetic resonance angiography (MRA), computed tomographic angiography (CTA), and extracranial and transcranial Doppler ultrasound are rapidly replacing contrast angiography for the diagnosis of cervicocephalic arterial dissections, particularly in cases of carotid artery involvement (eFig. 65.10).





eFig. 65.10 Following intravenous administration of iodinated contrast, spiral computed tomography images were obtained using 1.3-mm collimation and 0.5-mm image reconstruction intervals. Pseudoaneurysm of left internal carotid artery is noted, measuring 1.9 × 2.9 cm in greatest axial dimensions. There is calcification in the wall of the aneurysm. There is extensive mural thrombus such that the aneurysm lumen containing contrast measures 12.5 × 10.7 mm (*). Internal carotid artery is severely narrowed just proximal to its entry site into the aneurysm.

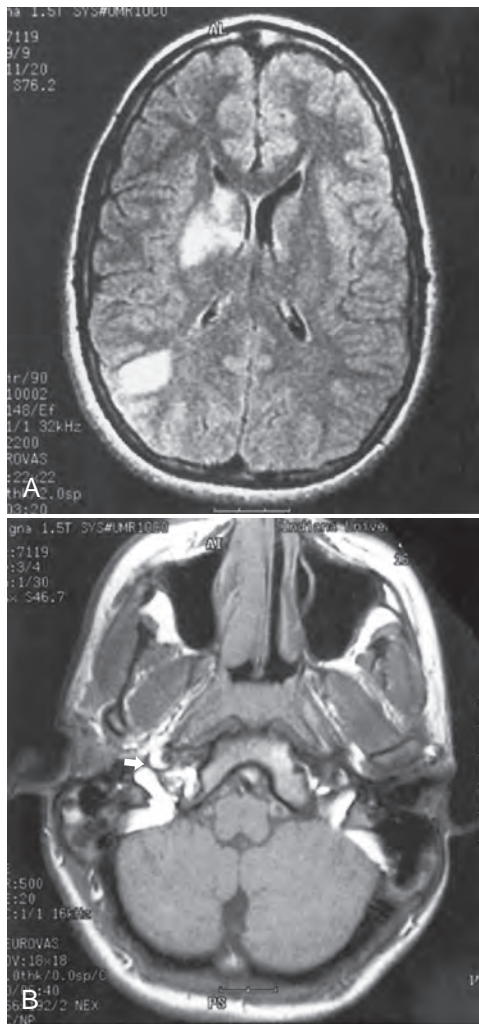


Fig. 65.12 A 16-year-old boy collapsed to the ground after experiencing right eye pain and left-sided weakness. **A**, Axial T2-weighted magnetic resonance imaging of the brain shows ischemic areas in the right basal ganglia and right posterior parietal region, associated with a crescentic sign (arrow in **B**) of high signal consistent with intraluminal blood products on the right internal carotid artery suggestive of a dissection.

Features on arteriography include the presence of a “pearl-and-string” sign; double-lumen sign; short, smooth, tapered occlusion; or pseudoaneurysm formation (eFig. 65.11). MRI demonstrates the intramural hematoma within the false lumen of the dissected artery (Fig. 65.12). MRA, CTA, or ultrasound studies can be helpful in monitoring the course of dissection.

Although the optimal antithrombotic regimen after cervicocephalic dissections is uncertain, reasonable therapeutic interventions have included immediate anticoagulation with heparin, followed by a 3- to 6-month course of warfarin or platelet antiaggregants. Angioplasty and stenting or surgical correction is reserved for selected individuals with pseudoaneurysms or those who have multiple recurrent events following adequate medical therapy. Although anticoagulants are often empirically recommended, their value in patients with extracranial cervicocephalic arterial dissections has not been established. Anticoagulation should be withheld in patients with intracranial dissections (particularly involving the vertebrobasilar circulation) because of the risk

for subarachnoid hemorrhage. The Cervical Artery Dissection in Stroke Study (CADISS). A randomized multicenter open-treatment trial comparing anticoagulant and antiplatelet therapies for acute (within 7 days) symptomatic extracranial carotid or vertebral artery dissection found no difference in efficacy of these classes of drugs at preventing stroke and death (The CADISS trial investigators, 2015).

Trauma

Trauma is a leading cause of cerebrovascular mortality in the United States (see Chapter 62). Blunt or penetrating traumatic cerebrovascular disease may result in cervicocephalic arterial dissection, arterial thrombosis, arterial rupture, pseudoaneurysm formation, or development of an arteriovenous fistula. Internal carotid artery thrombosis also may follow maxillary and mandibular angle fractures. Carotid artery trauma may cause hematoma formation of the lateral neck, retinal or hemispheric ischemia, and post-ganglionic Horner syndrome. Neurological deficits may be mild or devastating. Comatose patients with carotid arterial injuries with a Glasgow Coma Scale score of 8 or less do poorly regardless of treatment (see Chapter 5). Missing the diagnosis may lead to devastating results. A thorough evaluation of the airway, oropharynx, and esophagus is needed. Arteriography is indicated in most instances, although CTA has become a preferred screening modality for diagnosis; thereafter, surgical repair or angioplasty may be needed (Nuñez et al., 2004).

Radiation Vasculopathy

Injury to the endothelial cells by high-intensity radiation may cause accelerated atherosclerotic changes, particularly in the presence of hyperlipidemia. These changes may occur months to years after completion of radiation therapy. Radiation vasculopathy correlates with radiation dose and age at time of radiation therapy. Lesions develop in locations that are unusual for atherosclerosis and may involve the extracranial or intracranial vessels. Patients who receive therapeutic radiation therapy for lymphoma, Hodgkin disease, or thyroid carcinoma are at risk for involvement of the extracranial circulation. Follow-up carotid ultrasound and MRI studies are recommended in these patients. Radiation therapy also may cause an occlusive vasculopathy of small and large intracranial arteries following irradiation of intracranial neoplasms. Intracranial arterial stenosis also may follow stereotactic radiosurgery.

Moyamoya

Moyamoya is a chronic progressive nonatherosclerotic, non-inflammatory, nonamyloid occlusive intracranial vasculopathy of unknown cause. Pathologically, there is fibrocellular intimal thickening, smooth muscle cell proliferation, and increased elastin accumulation, resulting in stenosis of the supraclinoid intracranial internal carotid arteries. There is also thinning of the media and a tortuous and often multilayered internal elastic lamina. Thrombotic lesions may be seen in major cerebral arteries. There are also numerous perforating and anastomotic branches around the circle of Willis. Intracranial aneurysms may be seen at the circle of Willis or in the peripheral vessels. Moyamoya disease is sometimes distinguished from moyamoya syndrome associated with a number of different putative causes. Cases have been associated with neonatal anoxia, trauma, basilar meningitis, tuberculous meningitis, leptospirosis, cranial radiation therapy for optic pathway gliomas, neurofibromatosis type 1, tuberous sclerosis,



eFig. 65.11 Digital subtraction angiography demonstrating internal carotid artery dissection.

encephalotrigeminal angiomas (Sturge-Weber syndrome), phakomatosis pigmentovascularis type IIIb, brain tumors, FMD, polyarteritis nodosa, Marfan syndrome, Turner syndrome, pseudoxanthoma elasticum, hypomelanosis of Ito, Williams syndrome, cerebral dissecting and saccular aneurysms, sickle cell disease, β -thalassemia, Fanconi anemia, hereditary spherocytosis, lupus anticoagulant, Sneddon syndrome, homocystinuria, oral contraceptives, factor XII deficiency, type I glycogenosis, reduced form of nicotinamide adenine dinucleotide phosphate (NADP)-coenzyme Q reductase deficiency, renal artery stenosis, Down syndrome, Apert syndrome, Graves' disease, coarctation of the aorta, Alagille syndrome, hyperphosphatasia, Schimke immuno-osseous dysplasia, primary oxalosis, pulmonary sarcoidosis, and Hirschsprung disease.

Moyamoya disease may cause TIAs, including hemodynamic paraparetic TIAs secondary to watershed paracentral lobule ischemia, headaches, seizures, movement disorders (chorea, hemidystonia, hemichoreoathetosis), mental deterioration, cerebral infarction, or intracranial hemorrhage. TIAs are often precipitated by crying, blowing, or hyperventilation.

Moyamoya disease has a bimodal age distribution, with peaks in the first and fourth decades of life. Childhood moyamoya is characterized by ischemic manifestations, whereas adult moyamoya disease presents with hemorrhagic manifestations. Moyamoya affects children, adolescents, and young adults most frequently. Diagnosis is based on a distinct arteriographic appearance as described by Suzuki's 6 angiographic stages: (1) stenosis of the carotid fork, (2) initial appearance of moyamoya vessels at the base of the brain, (3) intensification of moyamoya vessels, (4) minimization of moyamoya vessels, (5) reduction of moyamoya vessels, and (6) disappearance of moyamoya vessels (collaterals only from external carotid arteries) (Fig. 65.13). Moyamoya is characterized by progressive bilateral stenosis of the distal internal carotid arteries, extending to the proximal ACA and MCA, with development of an extensive collateral (parenchymal,

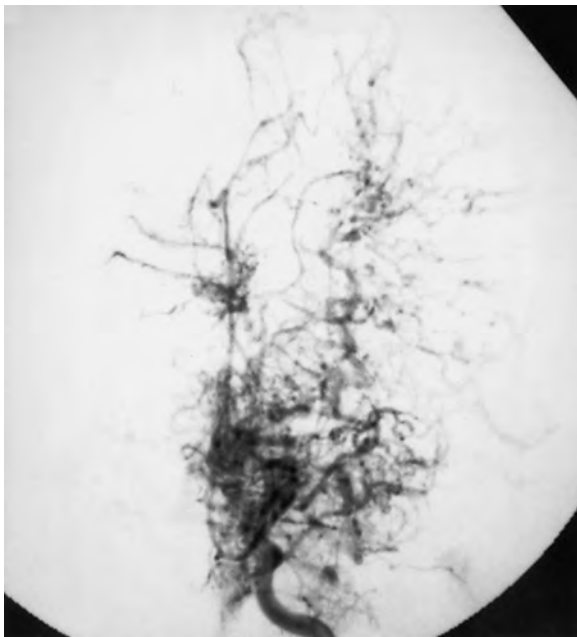


Fig. 65.13 Left carotid angiogram (anteroposterior view) shows occlusion of the supraclinoid internal carotid artery and innumerable moyamoya vessels. (Courtesy Vincent Mathews, MD.)

leptomeningeal, and transdural) network at the base of the brain like a cloud or puff of smoke (moyamoya). Intracranial aneurysms, particularly located in the posterior circulation, may be present.

The optimal treatment of ischemic moyamoya has not been determined. Platelet antiaggregants, vasodilators, calcium channel blockers, and corticosteroids have been used with variable results. Anticoagulants are not useful. Good results have been reported with superficial temporal artery to MCA anastomosis and other indirect or combined surgical revascularization procedures. No clear superior therapy to prevent rebleeding has been shown in the hemorrhagic type of moyamoya disease.

Fibromuscular Dysplasia

Fibromuscular dysplasia is a segmental, nonatheromatous, dysplastic, noninflammatory angiopathy affecting predominantly young and middle-aged women. Cervicocephalic FMD affects less than 1% of the population, occurs more often in whites than in blacks, and predominantly involves the cervical carotid arteries at the level of the C1 to C2 vertebral bodies. FMD of the intracranial arteries is rare and mainly limited to the intrapetrous internal carotid artery or carotid artery siphon. The cause of FMD is unknown. Immunological and estrogenic effects on the arterial wall may be causal mechanisms. An association with α_1 -antitrypsin deficiency has been reported. Four distinct histological types are recognized: intimal fibroplasia, medial hyperplasia, medial fibroplasia, and perimedial dysplasia. Medial fibroplasia is the most frequent form of FMD, followed by perimedial dysplasia and intimal fibroplasia. The majority of cases of FMD involve the renal arteries, followed by the carotid and iliac arteries. The subclavian and vertebral arteries are affected less commonly. Some cases are familial. Most often, patients with cervicocephalic FMD are asymptomatic or present with headaches, neck pain, carotidynia, tinnitus, vertigo, asymptomatic carotid bruits, transient retinal or cerebral ischemia, cerebral infarction, or subarachnoid hemorrhage. Cervicocephalic FMD may be associated with arterial dissection. Hypertensive patients may have concomitant renal FMD. Cerebral ischemia is usually related to the underlying arterial stenosis or arterial thromboembolism.

The diagnosis of cervicocephalic FMD may be made on the basis of MRA, CTA, or conventional catheter cerebral angiography. Cervicocephalic FMD occurs most often in the extracranial carotid artery and is bilateral in approximately two-thirds of cases. The lesions of medial fibroplasia account for the characteristic "string of beads" angiographic appearance seen in approximately 90% of cases (Fig. 65.14).

The optimal treatment of symptomatic cervicocephalic FMD has not been determined. In view of the benign natural history of this condition, platelet antiaggregants are recommended. Surgical intervention with angioplasty and stenting, gradual arterial dilatation, resection and reconstruction, or interposition grafting is seldom warranted.

Inflammatory Vasculitides

Inflammatory vasculitides can involve any size of vessel, including the precapillary arterioles and postcapillary venules. Many infectious and multisystem noninfectious inflammatory diseases cause cerebral vasculitis (see Box 65.4). Cerebral vasculitis is a consideration in young patients with ischemic or hemorrhagic stroke; patients with recurrent stroke; elderly patients with mental status or cognitive changes and leptomeningeal enhancement on imaging (Nouh et al., 2014); patients with stroke associated with encephalopathic features; and



Fig. 65.14 Lateral left carotid angiogram in a patient with fibromuscular dysplasia. Note "string of pearls" appearance around the C2 level.

patients with stroke accompanied by fever, multifocal neurological events, mononeuritis multiplex, palpable purpura, or abnormal urinary sediment. Other manifestations of cerebral vasculitis include headaches, seizures, and cognitive deterioration. Laboratory studies typically show anemia of chronic disease, leukocytosis, and an elevated erythrocyte sedimentation rate. The diagnosis of vasculitis usually requires confirmation by arteriography or biopsy. Overall, these disorders have a poor prognosis, but corticosteroids and other immunosuppressive agents have improved the survival rate (Biller and Grau, 2004).

Infections and Stroke

Intracranial vasculitis and stroke can result from meningovascular syphilis; prodromal manifestations are common before stroke. The MCA territory is most commonly affected. Spinal cord infarction may result from meningomyelitis. Other neurological manifestations in patients with secondary syphilis include headaches, meningismus, mental status changes, and cranial nerve abnormalities. The cerebrospinal fluid (CSF) may show a modest lymphocytic pleocytosis, elevated protein content, and a positive Venereal Disease Research Laboratory (VDRL) test result. Concurrent human immunodeficiency virus (HIV-1) infection can lead to rapid progression of early syphilis to neurosyphilis. Luetic aneurysms of the ascending aorta can extend to involve the origin of the great vessels and lead to stroke. Treatment schedules for syphilis are listed in standard textbooks; patients with concurrent HIV-1 infection and meningovascular syphilis may require prolonged antibiotic treatment.

Worldwide, an estimated 1 billion people are infected with *Mycobacterium tuberculosis*. Neurotuberculosis affects predominantly the basilar meninges. Predisposing conditions include alcoholism, substance abuse, corticosteroid use, and HIV-1 infection. Strokes can result from tuberculous endarteritis. The exudative basilar inflammation entraps the cranial nerves at the base of the brain, most frequently the third, fourth, and sixth cranial nerves. The basilar arteriolitis most commonly

involves penetrating branches of the ACA, MCA, and PCA (medial and lateral lenticulostriate, anterior choroidal, thalamoperforators, and thalamogeniculate arteries). There is usually a modest lymphocytic and mononuclear pleocytosis. The CSF protein is usually elevated, and the glucose level is depressed. In the early stages, a predominantly neutrophilic response may be noted. Smears of CSF demonstrate *M. tuberculosis* in 10% to 20% of cases. Polymerase chain reaction testing of CSF for mycobacterium tuberculosis DNA may aid the diagnosis. Repeated CSF examinations increase the yield considerably.

Fungal arteritis may result in aneurysms, pseudoaneurysms, thrombus formation, and cerebral infarction. Complications of acute purulent meningitis include intracranial arteritis and thrombophlebitis of the major venous sinuses and cortical veins. Intracranial arterial stenoses have been associated with a complicated clinical course. Varicella-zoster may cause a virus-induced necrotizing arteritis similar to granulomatous angiitis. Cerebral infarction is a complication of acquired immunodeficiency syndrome (AIDS) and may result from vasculitis, meningovascular syphilis, varicella-zoster virus vasculitis, opportunistic infections, infective endocarditis, aneurysmal dilation of major cerebral arteries, nonbacterial thrombotic endocarditis, aPL antibodies, or other hypercoagulable states, or from hyperlipidemia resulting from protease inhibitors and other factors such as HIV-1-related malignancy, cancer chemotherapy, and thrombotic thrombocytopenic purpura (TTP). Large-artery cerebrovascular occlusions have been found in association with meningoencephalitis caused by free living amebae. Other infectious agents known to produce cerebral infarcts include *Mycoplasma pneumoniae*, aspergillus, coxsackie 9 virus, California encephalitis virus, mumps paramyxovirus, hepatitis C virus, *Borrelia burgdorferi*, *Rickettsia typhi* group, cat-scratch disease, *Trichinella* infection, and the larval stage (cysticercus) of *Taenia solium*. Cerebrovascular involvement in neurocysticercosis is usually ischemic and is caused by chronic meningitis, arteritis, or endarteritis of small vessels. Unilateral or bilateral carotid artery occlusion can complicate necrotizing fasciitis of the parapharyngeal space. Infection with *Chlamydia pneumoniae* accelerates the process of atherosclerosis in animal studies; treatment with azithromycin has been shown to reduce the degree of atherosclerotic lesions in a rabbit model.

Drug Abuse and Stroke

Ischemic stroke is a complication of illicit drug use and use of over-the-counter sympathomimetic drugs. Stroke mechanisms associated with the use of illicit drugs are multifactorial, including foreign-body embolization, vasculitis, vasospasm, acute onset of arterial hypertension or arterial hypotension, endothelial damage, accelerated atherosclerosis, hyper- or hypocoagulability, cardiac arrhythmias, embolism from an MI, or AIDS. The substances implicated most commonly are the amphetamines, cocaine (freebase or "crack"), phenylpropanolamine, pentazocine (Talwin) in combination with Pyribenzamine ("T's and blues"), phencyclidine, heroin, anabolic steroids, and glue sniffing. Ischemic or hemorrhagic strokes may follow within hours of cocaine use, whether the drug is smoked, snorted, or injected (Fig. 65.15) (see Chapters 69 and 86). The risk for intracerebral hemorrhage, especially among young women, has led to removal from the American market of phenylpropanolamine. Ephedra, also called *ma-huang*, widely used in weight-loss products, has been associated with high blood pressure, heart attacks, and strokes. Stroke in young athletes may also be the result of anabolic-androgen steroid abuse and recombinant erythropoietin ("blood doping") administration.

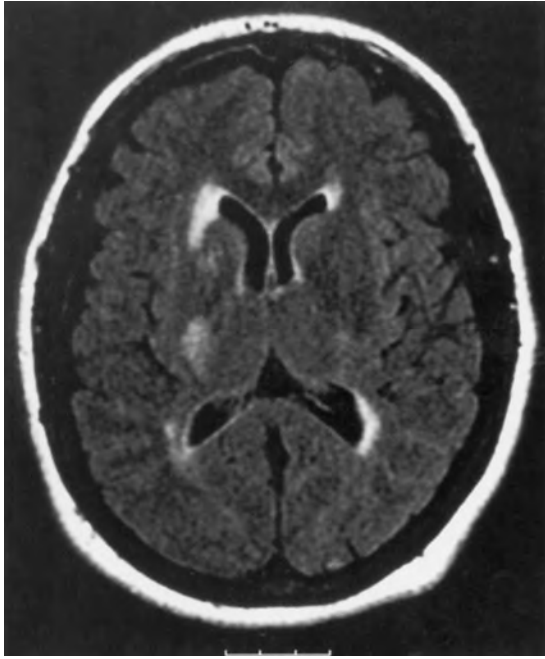


Fig. 65.15 A 41-year-old woman with a history of cocaine abuse had acute onset of left-sided hemiplegia, left hemibody sensory deficit, and a left homonymous visual field deficit. Axial fluid-attenuated inversion recovery image of the brain demonstrates an area of infarction in the posterior limb of the right internal capsule in the distribution of the anterior choroidal artery territory. There is associated periventricular ischemia.

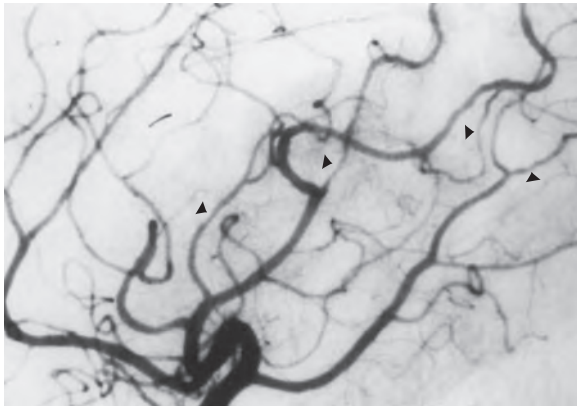


Fig. 65.16 Lateral carotid angiogram demonstrates irregular beading appearance (*arrowheads*) of large and medium branches of the anterior, middle, and posterior cerebral arteries in a patient with systemic lupus erythematosus. (Courtesy Vincent Mathews, MD.)

Stroke and Systemic Vasculitides

Ischemic stroke is also a complication of a variety of multisystem vasculitides. Stroke in patients with systemic lupus erythematosus may be attributable to cardiogenic embolism (nonbacterial verrucous or Libman-Sacks endocarditis, which occurs in the ventricular surface of the mitral valve), aPL antibodies, or underlying vasculopathy, or nephrotic syndrome associated with lupus nephritis, or less often to an immune-mediated vasculitis (**Fig. 65.16**) (see Chapter 58).



Fig. 65.17 Computed tomographic angiogram demonstrating left subclavian stenosis in a 32-year-old woman with Takayasu arteritis.

Behçet syndrome may involve vessels of any size. Venous thrombosis is more frequent than occlusive arterial compromise. Affected patients are mainly of Mediterranean or East Asian origin and may have a history of iritis, uveitis, and oral, genital, and mucocutaneous ulcerations. Cerebrovascular complications include strokes, carotid aneurysm formation, and cerebral venous thrombosis. Cogan syndrome is a rare condition characterized by nonsyphilitic interstitial keratitis, vestibular dysfunction, and deafness. Complications include aortic insufficiency and mesenteric ischemia. The angiitic form of sarcoidosis primarily affects the eyes, meninges, and cerebral arteries and veins. Kohlmeier-Degos disease or malignant atrophic papulosis is a multisystem occlusive vasculopathy characterized by cutaneous, gastrointestinal, and neurological manifestations; it may be complicated by ischemic or hemorrhagic strokes. Cerebral vasculitis may also complicate the course of children with acute poststreptococcal glomerulonephritis. The multisystem vasculitides are described in more detail in Chapter 58.

Takayasu arteritis is a chronic inflammatory arteriopathy of the aorta and its major branches, as well as the pulmonary artery (**Fig. 65.17**). The cause is unknown, but an immune mechanism is suspected. The disease, prevalent in young women of Asian, Mexican, or Native American ancestry, develops insidiously, causing stenosis, occlusion, aneurysmal dilatation, or coarctation of the involved vessels. The disease has two phases. In the acute or “prepulseless” phase, nonspecific systemic manifestations are present. Patients have rashes, erythema nodosum, fever, myalgias, arthritis, pleuritis, carotidynia, and elevated erythrocyte sedimentation rate. Months or years later, the second or occlusive phase develops and is characterized by multiple arterial occlusions. Patients may have cervical bruits, absent carotid or radial pulses, asymmetrical blood pressure recordings, and arterial hypertension. Neurological symptoms result from CNS or retinal ischemia associated with stenosis or occlusion of the aortic arch and arch vessels, or arterial hypertension caused by aortic coarctation or renal artery stenosis. Visual disturbances are most often bilateral. The diagnosis can be confirmed by MRA or CTA, but the most accurate assessment still requires aortography (see **Fig. 65.18**).

Patients with active disease are treated with oral glucocorticoids; cyclophosphamide, azathioprine, or methotrexate

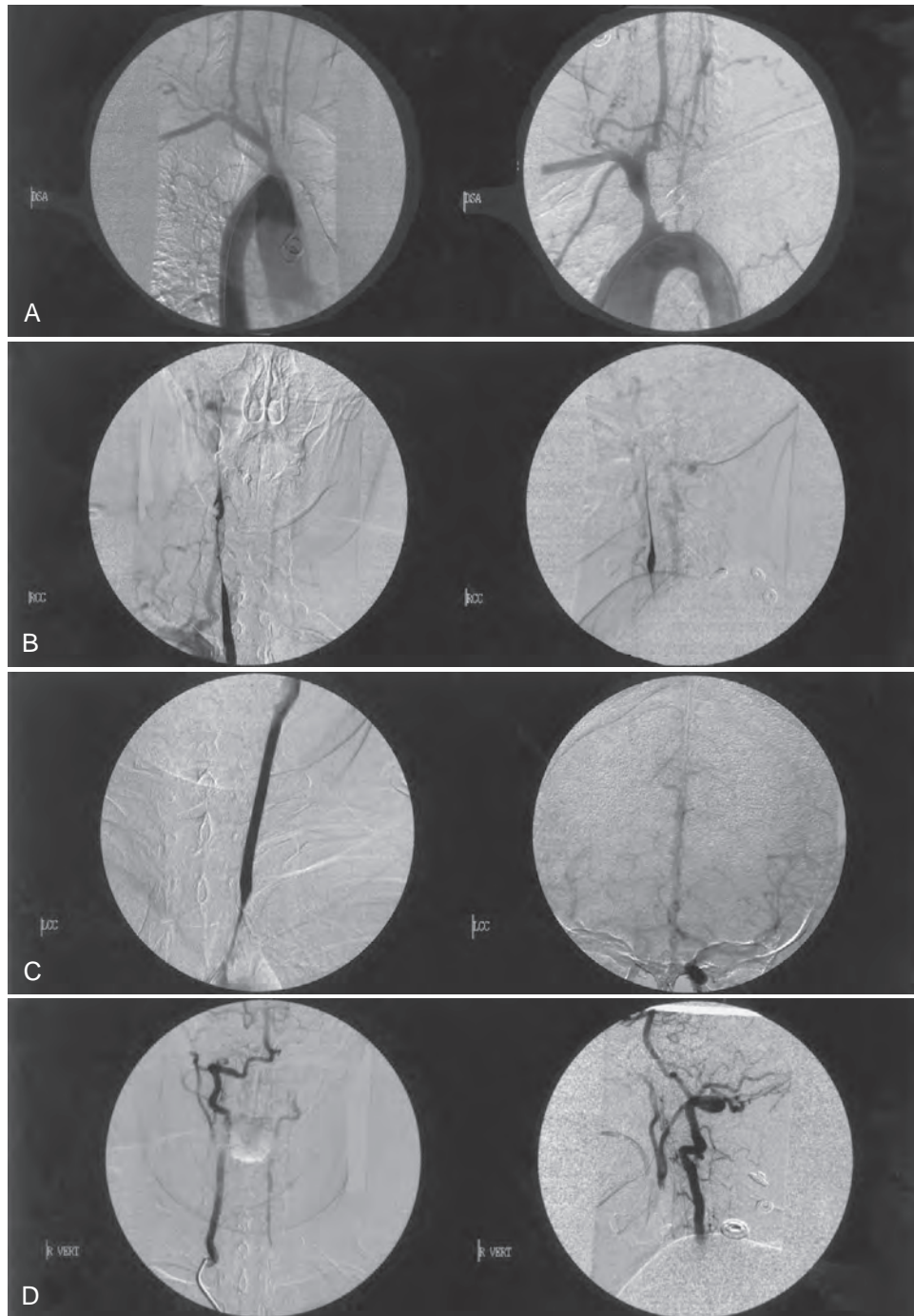


Fig. 65.18 **A**, Aortogram demonstrates a nonocclusive stenosis of the brachiocephalic artery. There is complete occlusion of the left subclavian artery. The left vertebral is absent or occluded. **B**, The right common carotid artery shows a long segment of critical stenosis extending from C3 to C5. **C**, There is also a very long stenosis of the left common carotid artery. **D**, A larger cervical right vertebral artery provides vigorous filling of the intracranial right internal carotid circulation.

may be needed in special circumstances. Surgical treatment (angioplasty or bypass) of severely stenotic vessels may be required.

Cranial (giant cell or temporal) arteritis is a polysymptomatic systemic large-vessel arteritis with a predilection to involve carotid artery branches (see Chapter 103). Thromboangiitis obliterans, also known as *Buerger disease*, is a rare segmental, inflammatory, obliterative angiopathy of unknown cause. The condition involves small and medium arteries and

veins. It is suspected in young men who smoke and have a history of superficial migratory thrombophlebitis presenting with distal limb ischemia accompanied by digital gangrene. The disorder is characterized by remissions and exacerbations. Cerebral involvement is uncommon. Strokes can result from isolated angiitis of the CNS including amyloid-beta related CNS angiitis. Symptoms of large-vessel involvement include stroke-like presentations. Small-vessel involvement may be manifested as a mass lesion in the brain or multifocal

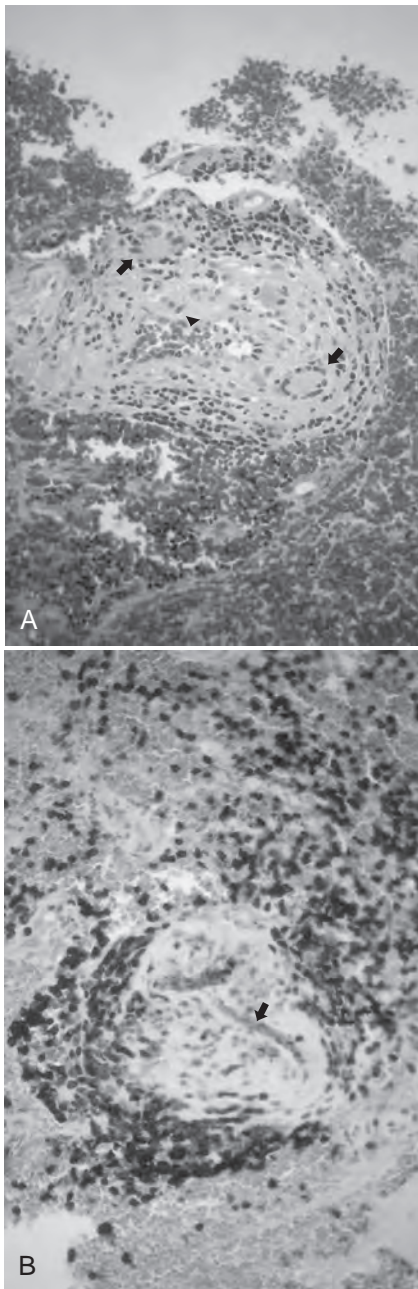


Fig. 65.19 Cerebellum. **A**, Within an area of recent hemorrhage, there is a small blood vessel showing focal infiltration with lymphocytes and a couple of multinucleated giant cells (arrows). Vessel lumen is marked with an arrowhead (hematoxylin and eosin, $\times 680$). **B**, Same vessel as in **A**. Immunostain with CD3 demonstrates intense perivascular infiltration with T lymphocytes ($\times 680$).

encephalopathy (Fig. 65.19). The erythrocyte sedimentation rate is usually normal or minimally elevated.

Migraine and Stroke

Migraine (see Chapters 20 and 103) affects women more often than men and may start during childhood or adolescence. Epidemiological studies suggest a nonrandom association of both headache and migraine with stroke, particularly among young women. The possible association between migraine headache and stroke was also evaluated by the Physician's

Health Study; physicians reporting migraine had increased risks of subsequent total stroke and ischemic stroke compared with those not reporting migraines (Buring et al., 1995). In the Women's Health Study, migraine with aura raised the risk of stroke by 108% (95% CI, 30%–231%). Migraine without aura raised the stroke risk by approximately 25%. The risk of MI was also increased (Kurth et al., 2005; Woodward, 2009). The risk of white-matter abnormalities on MRI is also increased, particularly among subjects with migraine with aura (Kruit et al., 2004). The risk of intracerebral hemorrhage is not increased in persons who have migraines.

The International Headache Society Classification and Diagnostic Criteria require that to establish a diagnosis of migrainous infarction, one or more migrainous aura symptoms must be present and not fully reversed within 7 days from onset, and must be associated with neuroimaging confirmation of ischemic infarction. This definition implies that a firm diagnosis of migraine with aura has been made in the past. Also, the clinical manifestations judged to be the result of a migrainous infarction must be those typical of previous attacks for that individual, and finally, other causes of infarction, including those related to migraine therapy need to be excluded by appropriate investigations.

Headache accompanies a number of embolic or thrombotic causes of stroke, including cervicocephalic arterial dissections. Migraines also can be a prominent symptom in the aPL antibody syndrome (APAS). Symptomatic migraine attacks are more frequent than migraine-induced ischemic insults. The presence of headache with a stroke is therefore not sufficient to make the diagnosis of migraine as the cause of the patient's symptoms. Furthermore, patchy subcortical abnormalities on MRI in patients with migraine with aura should be interpreted with caution. In other words, migrainous infarction remains a diagnosis of exclusion.

The pathogenesis of migrainous infarction is controversial. Cerebral infarcts complicating migraine are mostly cortical and involve the distribution of the PCA. The usual scenario of migrainous infarction is one of recurrent episodes of gradual buildup of unilateral throbbing headaches, associated with stereotyped visual phenomena occurring in both visual fields simultaneously, in one of which the vision loss becomes permanent. Migrainous infarctions have been subdivided as definite when all the International Headache Society criteria are fulfilled and possible when some but not all criteria are fulfilled. Patients with migrainous infarction are at increased risk for recurrent stroke.

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a familial nonarteriosclerotic, nonamyloid microangiopathy characterized by migraine with aura, recurrent subcortical ischemic strokes starting in mid-adulthood, leading to pseudobulbar palsy, cognitive decline, subcortical dementia, and early white matter hyperintensities on MRI (see Fig. 65.20). CADASIL is caused by simple missense mutations or small deletions in the Notch 3 gene on chromosome 19q12 encoding a transmembrane receptor Notch 3. The Notch 3 mutation has been thought to be one of the most common human mutations. Pathologically, there is a characteristic granular osmiophilic material in arterial walls, including dermal arteries. A subtype of migraine known as *familial hemiplegic migraine* and characterized by transient weakness or frank paralysis during the aura has also been mapped close to the CADASIL locus. The acronym, *CADASILM* (cerebral autosomal dominant arteriopathy with subcortical infarcts, leukoencephalopathy, and migraine), refers to a subvariety of CADASIL characterized by the high frequency of migraine. A clinical trial of donepezil in CADASIL patients with subcortical vascular cognitive impairment showed no improvement in general cognition, but

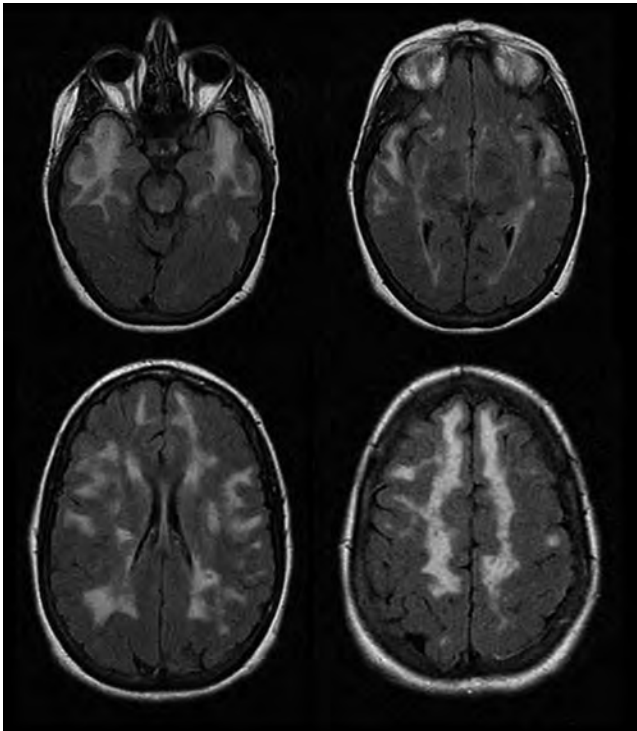


Fig. 65.20 Fluid attenuated inversion recovery (FLAIR) magnetic resonance imaging sequences of a patient with Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL).

improvement in some executive functions such as processing speed and attention (Schneider, 2008).

INHERITED AND MISCELLANEOUS DISORDERS

Homocystinuria, an inborn error of amino acid metabolism, is an unusual cause of stroke (Box 65.5). Three specific enzyme deficiencies responsible for homocystinuria have been identified: cystathionine- β -synthetase, homocysteine methyltransferase, and methylene tetrahydrofolate reductase. The accumulation of homocysteine in the blood leads to endothelial injury and premature atherosclerosis. Patients with homocystinuria may display a marfanoid habitus, malar flush, livedo reticularis, ectopia lentis, myopia, glaucoma, optic atrophy, psychiatric abnormalities, mental retardation, spasticity, seizures, osteoporosis, and a propensity for intracranial arterial or venous thrombosis. Death may result from pulmonary embolism, MI, or stroke. Raised levels of plasma homocysteine may be an independent risk factor for cerebrovascular disease, coronary artery disease, and peripheral arterial occlusive disease. Elevated levels of homocysteine can be effectively reduced with the administration of folic acid, occasionally requiring the addition of pyridoxine (vitamin B₆) and vitamin B₁₂. However, the treatment of high-normal homocysteine levels with folic acid and B-complex vitamins has not been associated with decreased stroke or coronary risk (Lonn et al., 2006; Toole et al., 2004). Other agents that may reduce homocysteine include choline, betaine, estrogen, and acetylcysteine.

Fabry disease is an X-linked disorder of glycosphingolipid metabolism characterized by deficient lysosomal α -galactosidase activity. As a result, deposits of ceramide trihexosidase accumulate in endothelial and smooth muscle cells. Patients have a painful peripheral neuropathy, renal disease, hypertension,

BOX 65.5 Inherited and Miscellaneous Disorders Causing Cerebral Infarction

Homocystinuria
 Fabry disease
 Marfan syndrome
 Ehlers-Danlos syndrome
 Pseudoxanthoma elasticum
 Sneddon syndrome
 Rendu-Osler-Weber syndrome
 Neoplastic angioendotheliomatosis
 Susac syndrome
 Eales disease
 Reversible cerebral segmental vasoconstriction syndrome
 Hypereosinophilic syndrome
 Cerebral amyloid angiopathy
 Coils and kinks
 Arterial dolichoectasia
 Complications of coarctation of the aorta
 Air, fat, amniotic fluid, bone marrow, and foreign particle embolism

cardiomegaly, autonomic dysfunction, and corneal opacifications. Characteristic dark red or blue lesions that do not blanch on pressure, called *angiokeratoma corporis diffusum*, are found between the umbilicus and knees. Stroke and MI are common. Female carriers may have mild disease or are asymptomatic.

Marfan syndrome is an autosomal dominant inherited connective tissue disease associated with qualitative and quantitative defects of fibrillin. Histopathological studies of aortic segments show cystic medial necrosis. This disorder is characterized by a variety of skeletal, ocular, and cardiovascular findings. Patients with Marfan syndrome may display arachnodactyly, extreme limb length, joint laxity, pectus excavatum or carinatum, subluxation of the lens, and aortic valvular insufficiency. Marfan syndrome is associated with a high incidence of dilatation of the aortic root. Other cardiovascular abnormalities include coarctation of the aorta, mitral valve prolapse, and mitral annulus calcification with regurgitation. Progressive dilatation of the aortic root may lead to dissection of the ascending aorta, resulting in ischemia to the brain, spinal cord, or peripheral nerves. Saccular intracranial aneurysms or dissection of the carotid artery can occur. Annual echocardiographic studies are recommended. Patients should avoid contact sports.

Patients with Ehlers-Danlos syndrome (see Chapter 105), a fairly common heritable connective tissue disorder, display hyperextensibility of the skin, hypermobile joints, and vascular fragility leading to a bleeding diathesis. Arterial complications have been reported in association with Ehlers-Danlos syndrome types I, III, and IV, especially type IV. Complications include dissections, arteriovenous fistulae, and aneurysms. Other cardiovascular abnormalities in patients with type IV Ehlers-Danlos syndrome include ventricular and atrial septal defects, aortic insufficiency, bicuspid aortic valve, mitral valve prolapse, and papillary muscle dysfunction. Arteriography carries special risks and should be avoided if possible.

Patients with pseudoxanthoma elasticum, an inherited group of disorders of elastic tissue, often display loose skin and small, raised, orange-yellowish papules resembling "plucked chicken skin" in intertriginous areas. Patients with pseudoxanthoma elasticum have a higher risk for coronary artery disease and MI. These patients may also have arterial hypertension, angiod streaks of the retina, retinal hemorrhages, arterial

occlusive disease, and arterial dissections. Women with pseudoxanthoma elasticum should avoid estrogens.

Sneddon syndrome consists of widespread livedo reticularis and ischemic cerebrovascular manifestations. A number of reports have documented a hereditary transmission and a link between Sneddon syndrome and aPL antibodies. An association with systemic lupus erythematosus (SLE) is also described. However, the etiopathogenesis remains unknown, although an immune mechanism is suspected. Endothelial cells could be the primary target tissue. Antiendothelial cell antibodies may be present.

Hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber disease) is a familial disorder transmitted as an autosomal dominant trait. Ischemic stroke as a presenting manifestation of Rendu-Osler-Weber disease has been reported infrequently. Paradoxical venous emboli passing through a pulmonary arteriovenous malformation can be the source of cerebral ischemia or abscess. Other potential causes leading to cerebral ischemia include air embolism and hyperviscosity secondary to polycythemia.

Neoplastic angioendotheliomatosis, also called *intravascular malignant lymphomatosis* or *angiotropic lymphoma*, is a rare disease characterized by multiple small- and large-vessel occlusions by neoplastic cell of lymphoid origin without an obvious primary tumor. Intravascular lymphomatosis has been reported to involve the skin, lungs, kidneys, adrenal glands, liver, pancreas, gastrointestinal tract, ovary, prostate, testicles, heart, thyroid, and parathyroid glands. Bone marrow, spleen, and lymph nodes are usually spared. Simultaneous involvement of blood vessels throughout the body and compromise of different cerebral arterial territories is common with this disorder. Patients may present with recurrent multifocal cerebral infarctions, dementia, or myelopathy. Diagnosis requires skin, liver, renal, or brain-leptomeningeal biopsy. Combination chemotherapy has been recommended. Autologous peripheral blood stem cell transplantation after chemotherapy may be useful.

Microangiopathy of brain, retina, and inner ear (Susac syndrome), also known as *retinocochleocerebral vasculopathy*, is a very rare microcirculatory syndrome that affects mainly adult women (Susac, 2004) (see Fig. 65.21). The syndrome is unrelated to arterial hypertension or diabetes and is characterized by arteriolar branch occlusions of the brain, retina, and inner ear, with resultant encephalopathy, vision loss, vestibular dysfunction, tinnitus, vertigo, and asymmetrical sensorineural hearing loss. CSF examination may be normal or show mild inflammatory response. MRI findings include multifocal white-matter hyperintensities with preferential involvement for the central fibers of the corpus callosum. Brain biopsy may show multifocal brain microinfarcts in both gray and white matter. The cause of Susac syndrome is unknown, but signs and symptoms have been attributed to a disturbance of coagulation, microembolism, or both. Treatment with corticosteroids, cyclophosphamide, azathioprine, plasmapheresis, or anticoagulant therapy is empirical, but branch retinal artery occlusions and CNS infarctions may recur despite the treatment. Hyperbaric oxygen treatment may be an option for refractory visual symptoms.

Eales disease, commonly reported in India and the Middle East, is a rare noninflammatory occlusive disease of the retinal vasculature characterized by repeated retinal and vitreous hemorrhages. The disorder affects mainly young men. Brain infarctions are rare.

Idiopathic reversible cerebral segmental vasoconstriction is an unusual clinical angiographic syndrome characterized by recurrent sudden high-intensity headaches (Call-Fleming syndrome) and transient motor and sensory findings associated with reversible arterial narrowing and dilatation involving

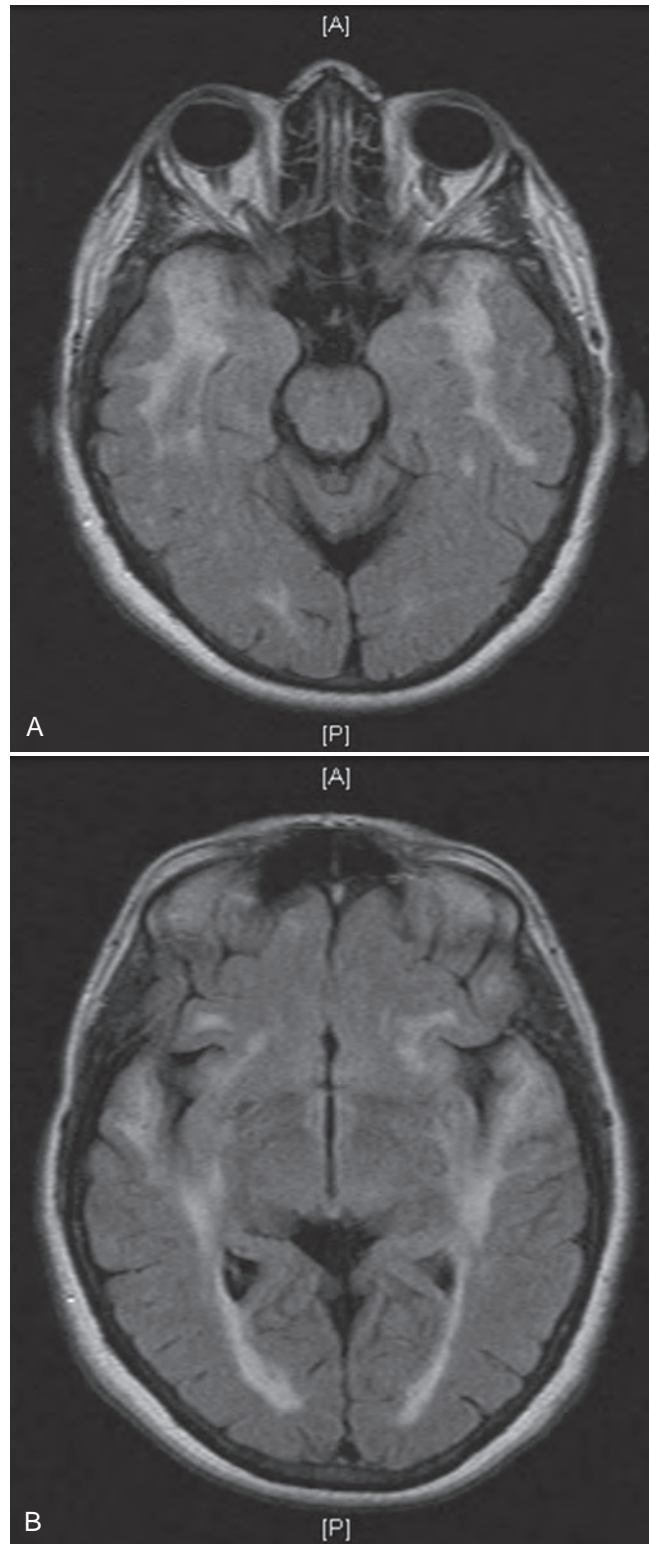


Fig. 65.21 Axial fluid attenuated inversion recovery magnetic resonance image sequence of a 53-year-old woman with Susac's syndrome showing characteristic lesions in the corpus callosum.

predominantly the arteries around the circle of Willis. The cause is unknown.

The hyper eosinophilic syndrome is a rare disorder caused by bone marrow overproduction of eosinophils that lodge in endothelial cells in the microcirculation primarily of heart, brain, kidney, lungs, gastrointestinal tract, and skin. Neurological complications include emboli from involved endocardium and heart valves, and neurological manifestations also may result from a hypercoagulable state with cerebral thromboses, and microcirculatory inflammation and occlusion by eosinophils. Cerebral infarction is a rare complication.

Cerebral amyloid angiopathy occurs both sporadically or in rare instances as a hereditary disorder. Cerebral amyloid angiopathy is characterized by the localized deposition of amyloid in the media and adventitia of small arteries and arterioles of the cerebral cortex and meninges in the elderly. Cerebral amyloid angiopathy is more commonly associated with lobar hemorrhage than with ischemic stroke, but it has been associated with an increased frequency of cerebral infarction in patients with Alzheimer disease. Biopsy of the involved cortex and leptomeninges is the only definitive way to diagnose cerebral amyloid angiopathy.

Redundant length of the cervical carotid artery causes coils and kinks and other forms of tortuosity. Occasionally associated with FMD, kinks and coils of the carotid artery are otherwise an infrequent cause of cerebral ischemia. Cerebral ischemia associated with kinking is due to a combination of flow reduction caused by obstruction, neck rotation, and distal embolization. Arterial kinking seldom affects the vertebrobasilar circulation, although there may be significant tortuosity of the vertebral or basilar arteries. Dolichoectasia, however, is an unusual vascular disease that causes enlargement and elongation of arteries, particularly the basilar artery. This arteriopathy causes a false aneurysm that leads to ischemic stroke, brainstem compression, cervicomedullary compression, cranial nerve palsies, cerebellar dysfunction, central sleep apnea, and hydrocephalus. The mechanisms of stroke are penetrating artery occlusion, basilar artery thrombosis, or embolism from the dolichoectatic artery.

Ischemic stroke and intracranial hemorrhage, the latter caused by arterial hypertension or ruptured intracranial aneurysm, are important complications of coarctation of the aorta. Spinal cord ischemia may also complicate surgery for aortic coarctation. Neurological complications also can result from aortic rupture, infective aortitis or endarteritis, associated aortic bicuspid valve, and dissection of the aorta proximal to the coarctation.

Atheromatous embolization (cholesterol emboli syndrome, blue toe syndrome, purple toe syndrome) may follow manipulation of an atherosclerotic aorta during catheterization or surgery. Clinical presentation may include TIAs, stroke, retinal embolism pancreatitis, renal failure, and livedo reticularis. Purple toes also may occur as a result of small cholesterol emboli lodging in the digital arteries. Pedal pulses are normal. Patients have a low-grade fever, eosinophilia, anemia, elevated erythrocyte sedimentation rate, and elevated serum amylase. Anticoagulation may exacerbate further embolization, and its use should be discouraged.

Accidental introduction of air into the systemic circulation can be a cause of cerebral or retinal ischemia. Air embolism is a dreaded complication of surgical procedures, including intracranial operations in the sitting position; open heart surgery; surgery of the lungs, pleura, sinuses, neck, and axilla; hemodialysis; thoracentesis; arteriography; central venous catheters; and scuba diving. Symptoms include seizures and multifocal neurological findings such as cerebral edema, confusion, memory loss, and coma. CT scan may be useful in visualizing the gaseous bubbles. Treatment includes prompt

resuscitative measures, placement of the patient in the left lateral position with head down, inotropic agents, anticonvulsants, anti-edema agents, and hyperbaric oxygen. Caisson disease can occur in persons who are scuba diving. Neurological features are due to multiple small nitrogen emboli that lead to ischemia of the brain and spinal cord; signs of spinal cord dysfunction are prominent. Hyperbaric oxygen therapy is the usual treatment.

Fat embolism to the brain complicates long-bone fractures, sickle cell disease, cardiopulmonary bypass, soft-tissue injuries, and blood transfusions. This syndrome occurs suddenly within hours to 3 or 4 days after injury and is characterized by dyspnea, fever, tachycardia, tachypnea, cyanosis, cutaneous petechiae, and coagulopathy. Neurological manifestations are confusion, disorientation, delirium, hemiparesis, aphasia, and coma. Petechial hemorrhages may be apparent on funduscopy, conjunctivae, base of the neck, and axillary region. Vigorous respiratory supportive therapy is essential.

Amniotic fluid embolism is a rare catastrophic obstetrical complication caused by the entry of amniotic fluid into the maternal bloodstream during parturition. Vigorous supportive therapy with intravenous (IV) fluids and blood replacement to treat shock, respiratory distress syndrome, disseminated intravascular coagulation (DIC), and underlying fibrinolytic state are essential. Among other causes of emboli are large intracranial saccular aneurysms or extracranial false aneurysms of the internal carotid artery. Tumor emboli to the brain have been reported with osteosarcoma, atrial myxoma, and carcinoma of the lung, breast, pharynx, or esophagus. Talc, cornstarch, and other foreign particles injected as adulterants in illicit drugs can embolize to the brain or retina. Paradoxical embolism during bone marrow infusion is an infrequent complication.

HYPERCOAGULABLE DISORDERS

Alterations in hemostasis are associated with an increased risk for cerebrovascular events, particularly those of an ischemic nature, and may account for a considerable number of cryptogenic strokes (Box 65.6). These disorders account for 1% of all strokes and 2% to 7% of ischemic strokes in young patients.

Primary Hypercoagulable States

Inherited disorders predisposing to thrombosis especially affect the venous circulation. These disorders include antithrombin deficiency, protein C and protein S deficiencies, activated protein C (APC) resistance, abnormalities of fibrinogen (dysfibrinogenemia), and abnormalities of fibrinolysis. Inherited thrombophilia should be suspected in patients with recurrent episodes of deep venous thrombosis, recurrent pulmonary emboli, family history of thrombotic events, unusual sites of venous (mesenteric, portal, or cerebral) or arterial thromboses, or in patients with thrombotic events occurring during childhood, adolescence, or early adulthood (deVeber et al., 2008). Approximately half of all thrombotic episodes occur spontaneously, although these patients are at greatest risk when exposed to additional risk factors such as pregnancy, surgery, trauma, or oral contraceptive therapy.

Antithrombin deficiency is inherited in an autosomal dominant fashion and affects both sexes. There are three categories of inherited antithrombin deficiency: classic or type I, characterized by decreased immunological and biological activity of antithrombin; type II, characterized by low biological activity of antithrombin but essentially normal immunological activity; and type III, characterized by normal antithrombin activity in the absence of heparin but reduced in heparin-dependent assays. Acquired antithrombin deficiency may follow acute

BOX 65.6 Hypercoagulable States**PRIMARY HYPERCOAGULABLE STATES**

Antithrombin deficiency
 Protein C deficiency
 Protein S deficiency
 Activated protein C resistance with or without factor V Leiden mutation
 Prothrombin G20210 mutation
 Dysfibrinogenemia
 Hypoplasminogenemia
 Abnormal plasminogen
 Plasminogen activators deficiency
 Antiphospholipid antibody syndrome (APAS)*

SECONDARY HYPERCOAGULABLE STATES

Malignancy
 Pregnancy/puerperium
 Oral contraceptive use
 Ovarian hyperstimulation syndrome
 Other hormonal treatments
 Nephrotic syndrome
 Polycythemia vera
 Essential thrombocythemia
 Paroxysmal nocturnal hemoglobinuria
 Diabetes mellitus
 Heparin-induced thrombocytopenia
 Homocystinuria
 Sickle cell disease (sickle cell anemia, sickle cell–hemoglobin C)
 Thrombotic thrombocytopenic purpura
 Chemotherapeutic agents

*APAS may be primary or secondary.

thrombosis and DIC. It also has been associated with nephrotic syndrome, liver cirrhosis, eclampsia, various malignancies, the use of estrogens or oral contraceptives, L-asparaginase, tamoxifen, and heparin therapy. A normal level of antithrombin activity obtained at the time of an acute thrombotic event is sufficient to exclude a primary deficiency. However, a low level of antithrombin activity must be confirmed by repeat testing after resolution of the thrombotic episode and discontinuation of anticoagulant therapy. Confirmation of a low plasma level of antithrombin activity on repeat testing is compatible with a primary deficiency and is an indication to investigate other family members. Thrombotic episodes associated with antithrombin deficiency are treated acutely with heparin, with or without adjunctive antithrombin concentrate. Prophylactic therapy in patients with recurrent thrombosis consists of long-term warfarin administration, keeping the therapeutic INR range between 2.0 and 3.0.

Protein C deficiency is inherited in an autosomal dominant fashion. Homozygous protein C deficiency presents in infancy as purpura fulminans neonatalis. Heterozygotes are predisposed to recurrent thrombosis. Thrombotic manifestations are predominantly venous. Acquired protein C deficiency has been associated with the administration of L-asparaginase, warfarin therapy, liver disease, DIC, postoperative state, bone marrow transplantation, and the adult respiratory distress syndrome. Testing for immunological and functional assays of protein C should be performed after oral anticoagulation has been discontinued for at least a week. Heparin does not modify the levels of protein C. Warfarin-induced skin necrosis is a serious potential complication of protein C-deficient patients at the initiation of warfarin therapy; this syndrome

often occurs in association with large loading doses of warfarin. However, this deficiency is rare, and routine heparin administration prior to warfarin initiation is not mandatory unless there is reasonable clinical suspicion of protein C deficiency. In that case, the acute management of thrombosis associated with protein C deficiency consists of prompt administration of heparin followed by incremental doses of warfarin, starting with low doses until adequate anticoagulation is achieved. Long-term management requires the administration of warfarin.

Protein S deficiency also has an autosomal dominant mode of inheritance. Protein S exists in plasma in two forms: approximately 40% of the total protein S is functionally active or free, and the remainder is complexed to a binding protein. Homozygous protein S deficiency presents with venous thromboembolic disease. Heterozygotes are prone to recurrent thrombosis, including cerebral venous thrombosis. Acquired protein S deficiency occurs during pregnancy, in association with acute thromboembolic episodes, DIC, nephrotic syndrome, systemic lupus erythematosus, and with the administration of oral contraceptives, oral anticoagulants, and L-asparaginase. Immunological assays of total and free protein S and functional assay of protein S should be confirmed after resolution of the thrombotic episode and discontinuation of oral anticoagulants. Heparin therapy is effective in managing acute thrombotic events associated with protein S deficiency, whereas warfarin is advocated for patients with recurrent thromboembolism.

Resistance to APC is one of the most common identifiable risk factors for venous thromboembolic disease, including cerebral venous thrombosis. The relation of APC resistance to arterial disease is not well established. APC resistance has been identified as being 5 to 10 times more common than deficiencies of antithrombin, protein C, or protein S. APC resistance also has an autosomal dominant mode of inheritance and is associated in most patients with a single point mutation in the factor V gene (factor V Leiden) that involves replacement of arginine 506 with glutamine 506 (Arg 506 Gln). Testing for resistance to APC must be done after discontinuation of anticoagulants. There are conflicting results about factor V Leiden gene mutation and the risk for acute cerebral arterial thromboses (Fields and Levine, 2005). The contribution of factor V Leiden or prothrombin G20210A to ischemic stroke in the young is less clear. Conversely, both factor V Leiden and prothrombin G20210A mutations are associated with an increased risk for cerebral venous thrombosis. In the Physicians' Health Study, no association between factor V Leiden or prothrombin G20210A and ischemic stroke was found (Ridker et al., 1995).

Abnormalities of fibrinogen account for approximately 1% of all inherited thrombotic disorders. Fibrinogen cross-links platelets during thrombosis and is an important component of atherosclerotic plaques. High concentrations of fibrinogen increase the risk for stroke and MI. Dysfibrinogenemia reflects a qualitative disorder in the fibrinogen molecule and may be associated with hemorrhagic or thrombotic episodes. Hereditary dysfibrinogenemia is inherited in an autosomal dominant fashion. Decreased concentrations of fibrinogen are associated with DIC, liver failure, snake bite, treatment with L-asparaginase, anacrod, fibrinolytic drugs, and valproate. Treatment consists of infusions of cryoprecipitate.

Decreased levels of plasminogen (hypoplasminogenemia), qualitative abnormalities in the plasminogen molecule (dysplasminogenemias), and defective release of plasminogen activators occur in families with recurrent thrombotic events. Cerebral venous thrombosis occurs with disorders of plasminogen. Prophylactic therapy in patients with recurrent thrombosis consists of lifelong anticoagulation.

Lupus anticoagulants and anticardiolipin (aCL) antibodies are known collectively as *antiphospholipid antibodies* and have a pathogenetic role in arterial and venous thrombosis. Ischemic stroke is the most common arterial thrombotic event in patients with APAS. APAS associates the presence of aPL antibodies in high titers with recurrent arterial or venous thromboses, fetal loss, and livedo reticularis. Several aPL antibodies have been described in immunoglobulin (Ig)G, IgA, or IgM isotypes: aCL, antiphosphatidylethanolamine (aPE), antiphosphatidylserine, and antiphosphatidylcholine. An association with β_2 -glycoprotein 1 antibodies has also been described. Affinity-purified aCLs do not bind to cardiolipin in the absence of serum or plasma. The component required for aCL binding is β_2 -glycoprotein 1 (β_2 GP1). It is the β_2 GP1-dependent aCL of the IgG isotype that has been significantly associated with strokes and myocardial infarcts (Brey et al., 2001). Other stroke studies have reported an association with aPE (Gonzales-Portillo et al., 2001).

Antiphospholipid antibodies are present in patients with systemic lupus erythematosus and related autoimmune disorders, Sneddon syndrome, acute and chronic infections (including HIV-1), neoplasias, inflammatory bowel disease, administration of certain drugs, early-onset severe pre-eclampsia, liver transplantation, and in individuals without demonstrable underlying disorders. A distinct group of patients has a primary APAS; its association with ischemic cerebrovascular disease is rare.

Antiphospholipid antibodies are associated with recurrent fetal loss, a prolongation of the activated partial thromboplastin time (aPTT) that does not correct on one-to-one mixing with normal plasma, thrombocytopenia, a false-positive VDRL test result, and livedo reticularis. They may also be associated with cerebral and ocular ischemia, cerebral venous thrombosis, migraine, vascular dementia, chorea, transverse myelopathy, MI, peripheral arterial thromboembolism, venous thrombosis, pulmonary embolism, and Degos disease. Multiple cerebral infarctions are common in patients with aPL antibodies; a subset of patients may present with vascular dementia (eFig. 65.22). Still another group may have an acute or progressive thrombotic ischemic encephalopathy. Pathological studies of cerebral arteries involved in association with aPL antibodies demonstrate the presence of a chronic thrombotic microangiopathy but no evidence of vasculitis. Patients with aPL antibodies have an increased frequency of mitral and aortic vegetations. There are findings resembling verrucous endocarditis (Libman-Sacks endocarditis). Left ventricular thrombus formation is a rare occurrence.

The diagnosis of APAS or Hughes syndrome requires high plasma lupus anticoagulant (LA) titers (in the absence of other coagulopathies), moderately high aCL IgG (>40 IgG plasma level), or anti- β_2 -glycoprotein IgG antibodies in serum or plasma on at least two occasions at least 12 weeks apart, measured by a standardized enzyme-linked immunosorbent assay (ELISA). Treatment for arterial thrombosis associated with aPL antibodies is not well established. The best therapeutic strategy for preventing stroke in patients with APAS remains uncertain. In patients who have stroke and APAS, aspirin is as effective as moderate-intensity warfarin for preventing cerebral ischemic events. In a prospective cohort study of a subgroup of patients with ischemic stroke in the Warfarin-Aspirin Recurrent Stroke Study trial, aspirin (325 mg) and warfarin (target INR 1.4–2.8) were equivalent for preventing recurrent strokes and venous thromboembolism (VTE) over a 2-year follow-up (Levine et al., 2004). To date, there is insufficient evidence to support the use of high-intensity warfarin (target INR > 3.0) over moderate-intensity warfarin in patients who have recurrent VTE. Because of its teratogenicity, warfarin should be avoided during pregnancy in patients with APAS

and replaced with low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH). Pregnant patients without a history of stroke are often treated with prednisone, low-dose aspirin, or both.

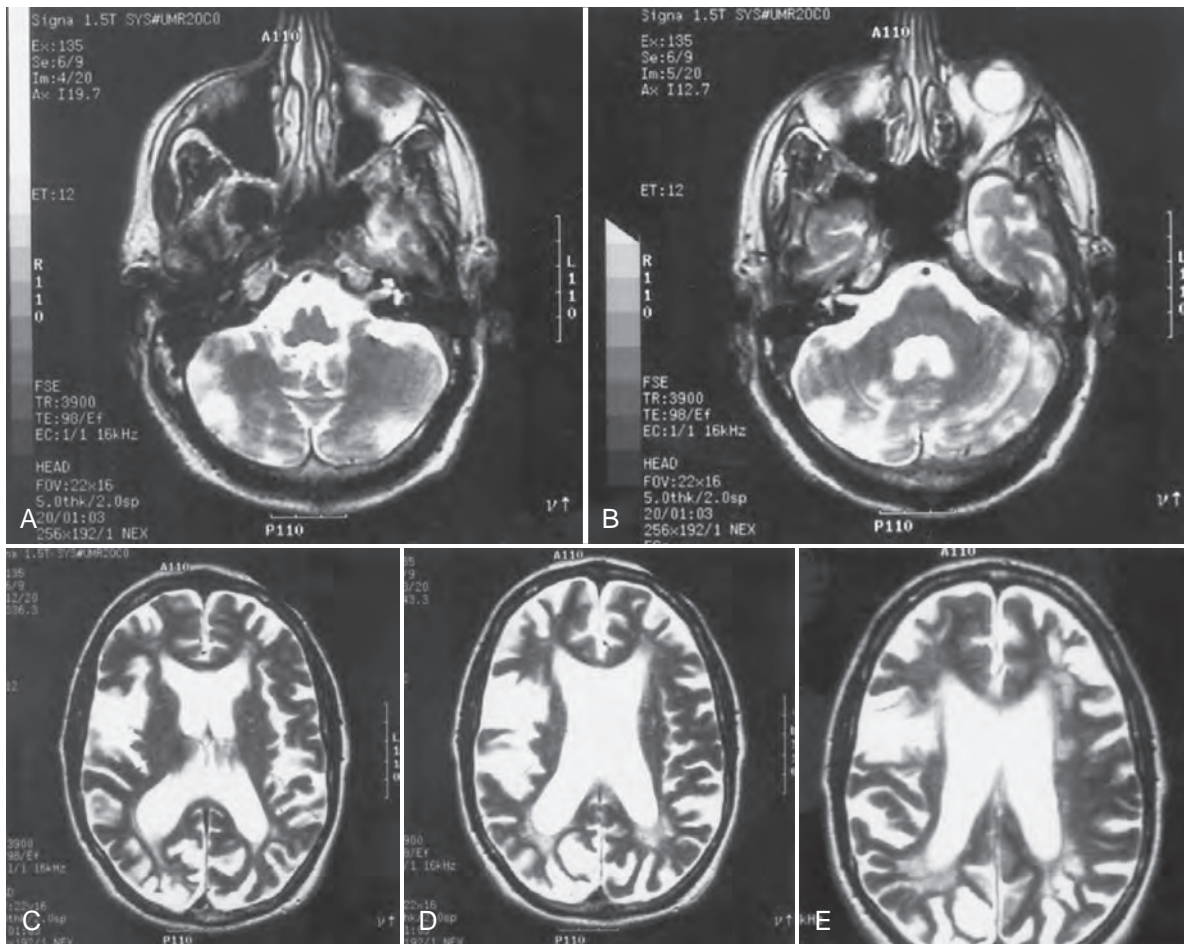
Secondary Hypercoagulable States

Strokes may complicate the clinical course of malignancies. In rare instances, stroke may be the initial manifestation of cancer. Cerebral infarction mostly complicates lymphomas, carcinomas, and solid tumors. Cerebral hemorrhages are more common with certain types of leukemia. Hypercoagulability is a common finding in patients with malignancy, especially myeloproliferative disorders, acute promyelocytic leukemia, brain tumors, and mucin-producing carcinomas of the pancreas, gastrointestinal tract, and lung. Mucinous adenocarcinomas of the gastrointestinal tract, lung, and ovary may produce infarcts from widespread cerebral arterial occlusions by mucin. The cause of the hypercoagulable state is often multifactorial. The pathophysiology may be due to a state of low-grade DIC and secondary fibrinolysis, but with the balance shifted toward clotting. Atherosclerosis is still the leading cause of infarction in patients with malignancy. Cerebral infarction in patients with malignancy also may be due to tumor emboli, bone marrow embolization, emboli originating from mural thrombi, or emboli arising from marantic vegetations associated with nonbacterial thrombotic endocarditis. Many patients with nonbacterial thrombotic endocarditis have associated DIC, which may cause capillary occlusion of multiple organs, especially the lungs, kidneys, gastrointestinal tract, heart, and brain. Neurological manifestations produce a diffuse encephalopathy secondary to disseminated microinfarcts. Other patients with malignancy and cerebral infarction may have cerebral venous occlusive disease caused by thrombi, tumor invasion, or stroke associated with chemotherapy. In addition, cancer-enhanced atherothrombosis, neoplastic angioendotheliomatosis, arterial compression by tumor, occlusive vascular disease secondary to irradiation, and intercurrent angitis may be responsible for cerebral infarction in some patients. Treatment consists of management of the underlying malignancy. Anticoagulants and platelet antiaggregants are used with variable success.

The postpartum period is a hypercoagulable state. Characteristically, arterial causes of stroke are more common during pregnancy, whereas venous causes of stroke are more common during the puerperium (see Chapter 112).

Oral contraceptives may cause alterations of the vessel wall, with intimal hyperplasia. They also may increase blood viscosity. There are decreased levels of protein S, antithrombin activity, and plasminogen activator content in women taking oral contraceptives. There also may be an increase in the levels of fibrinogen, factor VII, and factor X. Oral contraceptive therapy may enhance arterial hypertension. Women taking oral contraceptives have an estimated ninefold increased risk for thrombotic stroke. This risk is increased by prolonged use, high dosage of the estrogen component, cigarette smoking, concomitant diabetes, arterial hypertension, hyperlipidemia, and age older than 35 years. Current users of oral contraceptives are at increased risk for stroke; one study showed that oral contraceptives containing 30 μ g of estrogen are associated with a one-third reduced risk compared with preparations containing 50 μ g. The occurrence of intracranial venous thrombosis as a complication of oral contraceptives is well recognized. A patient on oral contraceptives occasionally presents with stroke secondary to paradoxical embolism associated with deep venous thrombosis.

Oral contraceptives probably should be avoided in women with arterial hypertension. They should also be



eFig. 65.22 A 44-year-old man with elevated anticardiolipin antibodies had a branch retinal vein occlusion in the left eye, progressive balance problems, poor memory, and an overall decline in cognitive functioning. Echocardiography showed a thickened mitral valve without significant stenosis. T2-weighted axial magnetic resonance imaging of the brain demonstrates confluent hyperintensities in the periventricular region and basal ganglia consistent with ischemia. There are also bilateral hyperintensities in the cerebellum consistent with infarcts. Cortical ischemic changes are also present bilaterally in the occipital lobes and in the right frontal lobe.

avoided in the first 2 weeks after delivery. Women older than 35 years who smoke cigarettes should be advised to consider a different contraceptive method. As part of primary stroke prevention efforts, women who smoke should not use oral contraceptives.

The ovarian hyperstimulation syndrome occurs in women after induction of ovulation with clomiphene, human menopausal gonadotropin, human follicle-stimulating hormone extracted from human pituitary, and human chorionic gonadotropin. Evidence of body-fluid shifts and hypercoagulability exists with this syndrome, contributing to thromboembolic events. Stroke is a rare but serious consequence of severe ovarian hyperstimulation syndrome.

Thromboembolic events are a complication of hormone treatment in transsexuals. Cerebral infarction has occurred as a side effect of exogenous estrogen in a male-to-female transsexual. Likewise, TIAs and cerebral infarction may follow the administration of anabolic steroids for the treatment of hypogonadism and hypoplastic anemias and performance-enhancing use in athletes. Cerebral ischemia also has occurred following the use of human recombinant erythropoietin in the treatment of anemia of patients on hemodialysis.

The nephrotic syndrome may be accompanied by venous and arterial thromboses, including cerebral arterial and venous occlusive disease. Ischemic stroke can be the presenting manifestation. The mechanism by which nephrotic syndrome causes hypercoagulability is multifactorial and includes elevated levels of fibrinogen; raised levels of factors V, VII, VIII, and X; thrombocytosis; enhanced platelet aggregation; and reduced levels of antithrombin and protein S. The exact role of hyperlipidemia, corticosteroids, and diuretic use is uncertain. Nephrotic syndrome should be considered as a contributing mechanism in any patient with ischemic stroke and pre-existing renal disease. A urinalysis is the initial clue to the diagnosis. The presence of severe proteinuria and a low serum albumin should prompt consideration of a hypercoagulable state. Treatment of thromboembolism associated with nephrotic syndrome consists of anticoagulants until remission of the renal condition.

Polycythemia vera and primary or essential thrombocythemia are typically disorders of middle-aged or elderly patients. Polycythemia vera is characterized by increased red blood cell mass and normal arterial oxygen saturation. Genomic studies have identified a mutation in the genetic sequence of a specific tyrosine kinase known as *Janus kinase* (JAK2). Patients have ruddy cyanosis, painful pruritus, hypertension, splenomegaly, elevated hemoglobin, high hematocrit value, thrombocytosis, leukocytosis, and elevated serum B₁₂ levels. Typically, the bone marrow is hypercellular. Secondary polycythemia may occur in association with cerebral hemangioblastoma, hepatoma, hypernephroma, uterine fibroids, benign renal cysts, carbon monoxide exposure, and administration of androgens. Cerebral blood flow is reduced and cerebral hemorrhage and arterial or venous thrombosis can complicate the condition. The majority of the intracranial events are thrombotic in origin, the larger cerebral arteries being the most frequently involved. The risk for stroke parallels the hemoglobin level: the higher the hemoglobin and hematocrit values, the greater the risk for stroke. Headaches, dizziness, vertigo, tinnitus, visual disturbances, carotid and vertebrobasilar TIAs, chorea, and fluctuating cognitive impairment are well-recognized features of patients with polycythemia vera. Spinal cord infarction is a rare complication. Spinal cord and optic nerve syndromes may also be due to extramedullary hematopoiesis. Cautious lowering of the hematocrit is a reasonable therapeutic approach. Because of the potential risk for hemorrhagic intracranial complications, aspirin therapy should be used cautiously.

Cerebral thrombotic and hemorrhagic complications are common in primary or essential thrombocythemia. Patients may have splenomegaly, mucocutaneous hemorrhagic diathesis, persistent elevated platelet count (usually in excess of 1 million/mL), giant platelets, and a bone marrow megakaryocyte hyperplasia. Frequent neurological complications include headaches, dizziness, amaurosis fugax, and TIAs of the brain. Cerebral arterial thrombosis caused by platelet-fibrin thrombi is a rare but serious complication of essential thrombocythemia. Papilledema secondary to cerebral venous thrombosis may be a complication in patients whose platelet levels have not been controlled. Cerebral infarctions also have been reported in patients with thrombocythemia secondary to iron-deficiency anemia. Iron-deficiency anemia with or without thrombocytosis has been implicated as a cause of intraluminal thrombus of the carotid artery, intracranial venous thrombosis, and intracranial hemorrhage. Thrombocytosis is common after splenectomy but does not seem to carry an increased thromboembolic risk. However, reactive thrombocytosis following cardiopulmonary bypass surgery may be involved in the cause of stroke in the late recovery period after surgery. The role of rebound thrombocytosis in ischemic stroke among heavy alcohol drinkers is uncertain. Treatment of primary thrombocythemia includes hydroxyurea, plateletpheresis, recombinant interferon alfa (IFN- α), and aspirin. Vigorous correction of the anemia is indicated for those patients with thrombocytosis associated with iron-deficiency anemia.

Paroxysmal nocturnal hemoglobinuria is an acquired clonal stem-cell disorder characterized by severe hemolytic anemia and hemosiderinuria. A feared complication is cerebral venous thrombosis. Thrombosis of major cerebral veins or dural sinuses and portal vein thrombosis are the most frequent causes of death. Acute thrombotic episodes involving the cerebral veins may be treated with thrombolytic agents, unless contraindicated, or anticoagulant therapy. High-dose cyclophosphamide and granulocyte-colony stimulating factor are being studied for the treatment of paroxysmal nocturnal hemoglobinuria.

Diabetes mellitus is a well-established risk factor for ischemic stroke. Diabetes associated with arterial hypertension or hyperlipidemia adds significantly to stroke risk. A variety of platelet, rheological, coagulation, and fibrinolytic abnormalities may play a role in the pathogenesis of stroke in diabetic patients. Numerous hemorheological disturbances appear to affect the development of diabetic microvascular disease and may contribute to cerebrovascular ischemic events. Hemorheological alterations producing increased blood viscosity may include increased fibrinogen values, increased hematocrit, elevated factors V and VII, increased platelet aggregation, increased platelet adhesion, increased release of β -thromboglobulin, decreased red blood cell deformability, and decreased fibrinolytic activity.

Heparin-induced thrombocytopenia can cause high morbidity and mortality from thrombotic complications. Heparin therapy may induce two types of thrombocytopenia. The most frequently observed is type I heparin-induced thrombocytopenia, which is a mild and benign condition with platelet counts around 100,000/mL. This thrombocytopenia tends to occur early and resolve spontaneously. Complications are rare. Type II heparin-induced thrombocytopenia is a major, albeit infrequent (<3% with UFH and <1% with LMWH), adverse side effect of heparin therapy, with a delayed onset (5–15 days after heparin administration). An immune-mediated disorder characterized by increased levels of platelet-associated IgG and IgM, it increases the risk for venous and arterial thrombotic complications involving the brain, heart, and limbs. Fatalities are high, and hemorrhagic complications are rare. Unlike drug-induced immune TTP, petechiae are not seen in cases of

heparin-induced thrombocytopenia with thrombosis. Prevention is paramount, requiring an optimal reduction of the time of exposure to heparin to less than 5 days when possible, and daily platelet counts during heparin administration. Treatment requires immediate discontinuation of heparin and initiation of recombinant hirudin or argatroban followed by oral anticoagulation for 3 to 6 months.

Elevated plasma homocysteine levels are an independent risk factor for atherosclerotic disease. Patients with high plasma homocysteine levels have a greater likelihood of occlusive disease of the extracranial carotid arteries, cerebral arteries, and peripheral vascular and coronary beds when compared with the general population. Diagnosis of hyperhomocysteinemia may be made by demonstrating elevated basal plasma levels of homocysteine or raised levels after methionine loading. Reduction of homocysteine levels in plasma requires supplementation with folate and vitamins B₆ and B₁₂. The Vitamin Intervention for Stroke Prevention (VISP) study failed to show a benefit for B-complex supplementation for prevention of recurrent stroke, however, and a similar lack of benefit was noted for coronary heart disease (Lonn et al., 2006; Toole et al., 2004). The Vitamins to Prevent Stroke (VITATOPS) study, one of the largest international trials investigating the benefits of homocysteine lowering in patients with recent TIAs or ischemic stroke, showed no significant benefit of supplementation with folic acid and vitamins B₆ and B₁₂ for secondary stroke prevention (Hankey, 2010). Homocystinuria is covered earlier in this chapter under Inherited and Miscellaneous Disorders.

Sickle Cell Disease

Cerebrovascular disease is a major cause of morbidity and mortality in patients with sickle cell disease. Strokes in sickle cell anemia (hemoglobin SS [HbSS]) patients manifest as ischemic strokes in children and as intracerebral and subarachnoid hemorrhage in adults. The most common presentations of stroke in patients with sickle cell disease are hemiparesis, seizures, language or visual impairments, and coma. Cognitive impairment may result from silent infarcts. Coma is more suggestive of intracranial hemorrhage than cerebral infarction. Patients at greatest risk for stroke are those with (HbSS) severe anemia, higher reticulocyte counts, and lower hemoglobin F levels. Sickle cell disease leads to a hyperviscous condition within the microvasculature. At low oxygen tensions, erythrocytes containing hemoglobin S assume a sickle-like appearance. Sludging in small vessels occurs, resulting in microinfarctions in the affected organs. Although there is pathological evidence that microvascular occlusion and sludging caused by sickling does occur in the brain, the clinical and neurodiagnostic findings are consistent with a large-vessel arterial occlusive (intimal hyperplasia with superimposed thrombosis) disease affecting the major intracranial arteries. Ischemic stroke frequently involves the arterial border zones between major cerebral arteries and adjacent deep white matter. Infarcts are more common in the ACA–MCA boundary zone. Sickle cell disease commonly causes a moyamoya-like angiographic pattern. Sickle cell disease may be accompanied by thrombotic cerebral infarction, cerebral venous occlusive disease, or subarachnoid, intracerebral, or intraventricular hemorrhage. Delayed intracranial hemorrhage may follow cerebral infarction and has been described as a complication of bone marrow transplantation. Spinal cord infarction is extremely rare. Neurological symptoms may be triggered by hypoxia, sepsis, dehydration, or acidosis.

The evaluation of the stroke patient with sickle cell anemia must be carefully individualized. Blood cell count, peripheral blood smear, hemoglobin electrophoresis, and sickling test are

essential. MRI, MRA, and transcranial Doppler studies are valuable investigations in sickle cell patients. Transcranial Doppler is useful in detecting the intracranial vasculopathy and may make it possible to detect patients at highest risk for cerebral infarction and to initiate treatment prior to stroke. Cerebral angiography can be done safely with the use of low-osmolar contrast media after partial exchange transfusion is performed, to avoid complications associated with contrast material. The Stroke Prevention Trial in Sickle Cell Anemia evaluated children with sickle cell anemia and no history of stroke (Adams et al., 1998). Children were screened with transcranial Doppler ultrasonography. The trial was prematurely stopped by the National Heart, Lung and Blood Institute after 11 strokes (10 cerebral infarctions and one cerebral hemorrhage) occurred among the standard of care group, while only one ischemic stroke occurred among the transfused group. Maintenance of hemoglobin S below 30% was effective in reducing the risk for cerebral infarction in children with sickle cell anemia. Meticulous hydration, adequate oxygenation, and analgesia are necessary. Iron overload may be prevented by subcutaneous chelation with deferoxamine. If snoring is also identified as a risk factor for stroke patients with sickle cell disease, a more aggressive approach to upper airway obstruction, including surgery, may be indicated.

Thrombotic Thrombocytopenic Purpura

Thrombotic thrombocytopenic purpura (TTP) is a life-threatening, generalized microcirculatory condition of undetermined cause, characterized by fever, thrombocytopenic purpura, microangiopathic hemolytic anemia, renal dysfunction, and fluctuating neurological signs. TTP is exceedingly rare, with a reported incidence of one person per 1 million annually. Most cases are idiopathic, but TTP also may be caused by drug exposure or may be associated with pregnancy and the postpartum state, connective tissue disorders, infective endocarditis, or neoplasms. The pathological response is due to widespread segmental hyaline microthrombi in the microvasculature. Neurological symptomatology is protean and may be fleeting although stroke may occur. Patients frequently have headaches, visual disturbances, cranial nerve palsies, delirium, seizures, aphasia, paresis, and coma. Treatment is with infusions of fresh frozen plasma, plasmapheresis, corticosteroids, and platelet antiaggregants, singly or in combination. If plasma exchange fails, splenectomy combined with corticosteroids and IV vincristine may be used.

INFARCTS OF UNDETERMINED CAUSE

Despite an extensive workup, in a considerable percentage of persons with ischemic stroke, a causal factor cannot be determined. This percentage is possibly higher in patients younger than 45 years. Some of these ischemic strokes may result from asymptomatic episodes of paroxysmal atrial fibrillation; electrophysiological testing may be useful under those circumstances. The role of thrombophilia is also often underrecognized and warrants more detailed investigation in selected patients. The risk for recurrence of stroke of undetermined cause appears to be slightly less than that of ischemic strokes of other types.

ESSENTIAL INVESTIGATIONS FOR PATIENTS WITH THREATENED STROKES

The diagnostic evaluation for all patients with TIAs or evolving ischemic stroke includes full blood cell count with differential white cell and platelet counts, prothrombin time (PT), APTT, plasma glucose level, blood urea nitrogen, serum creatinine,

BOX 65.7 Specialized Laboratory Tests for Thrombophilia

AT activity
 Protein C
 Protein S (total and free antigen levels)
 APC resistance
 Factor V Leiden
 Prothrombin gene (G20210 A) mutation
 Cardiolipin (IgG, IgM, IgA) antibodies
 β_2 -glycoprotein 1 (IgG, IgM, IgA) antibodies
 Lupus anticoagulant
 Fibrinogen
 Plasminogen
 Plasminogen activator inhibitor
 Plasmin functional activity
 Factors V, VII, VIII, IX, X, XI, and XIII levels
 Hemoglobin electrophoresis
 Plasma homocysteine
 MTHFR gene mutation

APC, Activated protein C; AT, antithrombin; Ig, immunoglobulin.

lipid analyses, urinalysis, and 12-lead ECG. Glycosylated hemoglobin (Hb A_{1c}) is measured in patients having or suspected of having DM. Chest roentgenography, laboratory tests for thrombophilia (Box 65.7), erythrocyte sedimentation rate, and luetic serologies should be considered in appropriate circumstances.

Neuroimaging

Initial brain imaging with emergent cranial CT or MRI is done in all patients because it may detect hemorrhagic or mass lesions that can present as a TIA or evolving stroke. If cerebellar or brainstem symptoms are present, CT should include thin cuts through the posterior fossa. MRI is superior to CT in cerebral ischemia but is not readily available for emergent use in many centers and may be contraindicated in some patients such as those with cardiac pacemakers. MRI is useful to delineate ischemic strokes, especially involving the brainstem or cerebellum, or lacunar strokes, because diffusion, perfusion, and gradient echo MR sequences can rapidly detect early ischemic and hemorrhagic lesions and also describe the amount of at-risk tissue (the “ischemic penumbra”). Approximately 10% to 40% of patients with TIA symptoms have evidence of cerebral infarction on CT, while about 40% to 60% of patients with TIA have evidence of ischemic injury on DW-MRI studies (Ay et al., 2002; Kidwell et al., 1999). Prolonged duration of TIA symptoms, particularly in those with symptoms lasting longer than an hour, may predict imaging evidence of ischemic injury. Attention to early CT signs of ischemic stroke in the MCA territory, such as loss of gray/white-matter differentiation, sulcal effacement, effacement of the Sylvian fissure, and obscuration of the lentiform nucleus, is critical. The intracranial large vessel segments are occasionally hyperdense in the noncontrast CT (dense MCA sign, Sylvian fissure dot sign, dense basilar artery) before the infarction becomes visible (Fig. 65.23). The dense MCA sign is indicative of a thrombotic or embolic occlusion of the MCA. The dense MCA sign often predicts a large cortical infarct but is not always a poor prognostic indicator. MRA visualizes blood flow in the major cerebral arteries at the level of the circle of Willis and the extracranial cervical internal carotid and vertebral arteries. The specificity and sensitivity of MRA is improved with administration of gadolinium. The sensitivity

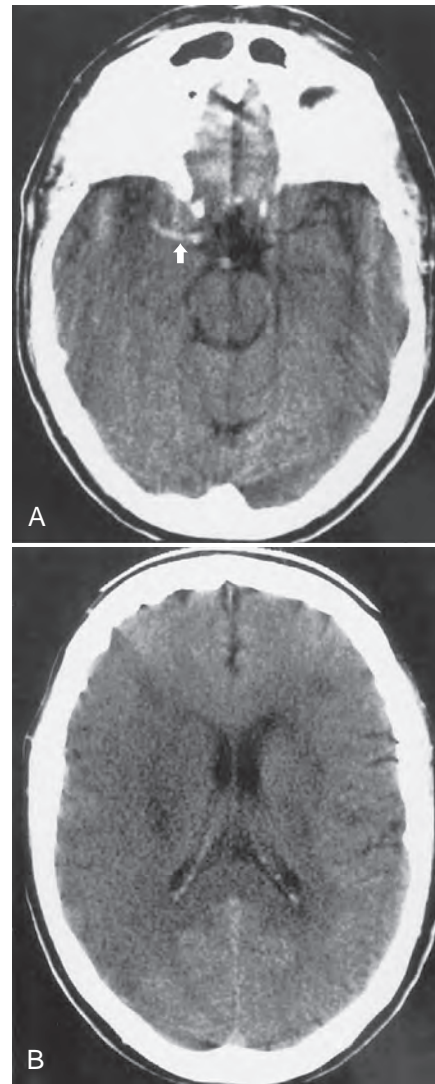


Fig. 65.23 Nonenhanced axial computed tomographic scans show (A) a dense right middle cerebral artery (MCA) sign (arrow) on the M1 segment and (B) a complete right MCA territory infarction. (Courtesy Vincent Mathews, MD.)

of MRI in differentiating infarction or other lesions from normal tissue depends primarily on changes in tissue T1 and T2 relaxation times, which are related to tissue water content (Figs. 65.24 and 65.25). DW-MRI allows early detection of acute cerebral ischemia while also differentiating acute from chronic stroke. Within the first 24 hours of an acute ischemic stroke, diffusion/perfusion mismatch may be present in as many as 70% of patients, complete ischemia in 10% to 20% of patients, and a reperfusion pattern in 10% to 15% of patients.

Advanced multifocal imaging with diffusion/perfusion or perfusion CT and CTA are increasingly being used to identify the ischemic penumbra (Eckert et al., 2011; Hopyan et al., 2010; Maas et al., 2009). Although the utility of diffusion/perfusion MRI for patient selection in the setting of thrombolytic therapy remains to be determined, studies support that diffusion/perfusion mismatches are indicative of brain at risk (Warach and Wardlaw, 2005). CT perfusion imaging is a modality that is increasingly being used to evaluate patients with acute ischemic stroke and may increase the likelihood for

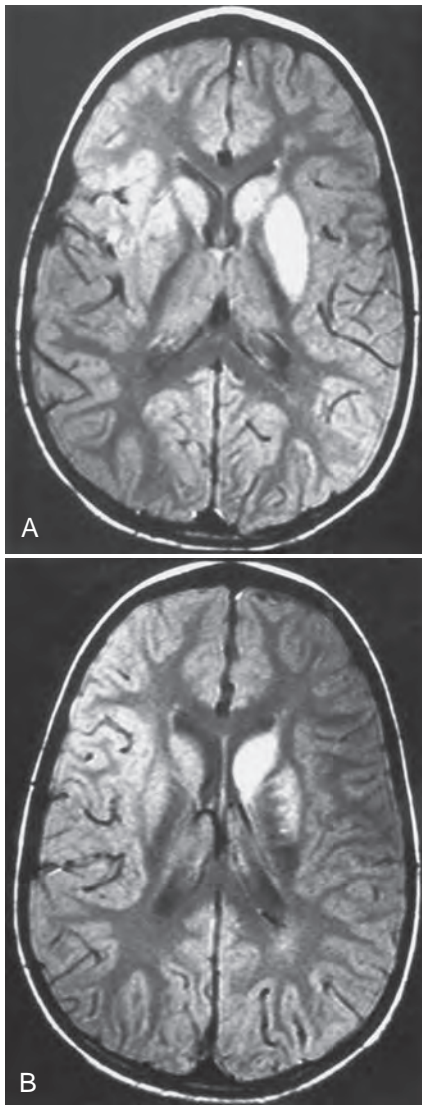


Fig. 65.24 Axial proton density magnetic resonance imaging demonstrates areas of increased signal intensity involving the head of the left caudate nucleus and the left lenticular nucleus, consistent with infarction. The internal portion of the globus pallidus is spared.

early diagnosis of stroke when used in addition to acute imaging protocols of noncontrast CT scan and CTA (Hopyan et al., 2010). CT perfusion imaging and CTA should be used selectively in stroke patients, because of the risks of increased radiation and contrast dye exposure (US Food and Drug Administration, 2010) (Fig. 65.26).

The emphasis in primary screening is on noninvasive testing, including Doppler imaging, B-mode scanning, duplex (combined B-mode and Doppler) scanning, and transcranial Doppler (TCD) imaging (see Chapter 40). In studies of duplex ultrasonography, sensitivity for detection of greater than 50% diameter stenosis ranged from 87% to 96%, and specificity ranged from 81% to 96%. There are, however, practical limitations of the ultrasound techniques. Severe stenosis or occlusion of an artery cannot be determined confidently by sonography. These methods also may fail to detect an intraluminal thrombus or a small atherosclerotic plaque, and some lesions are anatomically beyond the reach of the scanner. TCD assists in the evaluation of blood flow velocities and patency

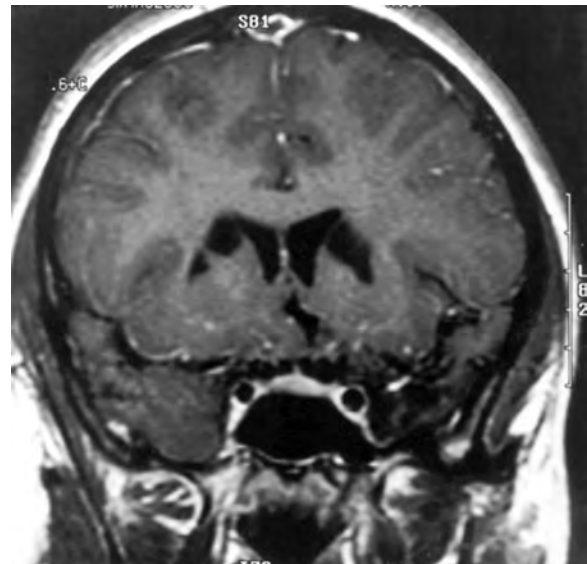


Fig. 65.25 Coronal T1-weighted magnetic resonance imaging with contrast of a 14-year-old boy demonstrates bilateral recurrent artery of Heubner territory infarcts with involvement of the head of the caudate nucleus and anterior limb of the internal capsule. (Courtesy Vincent Mathews, MD.)

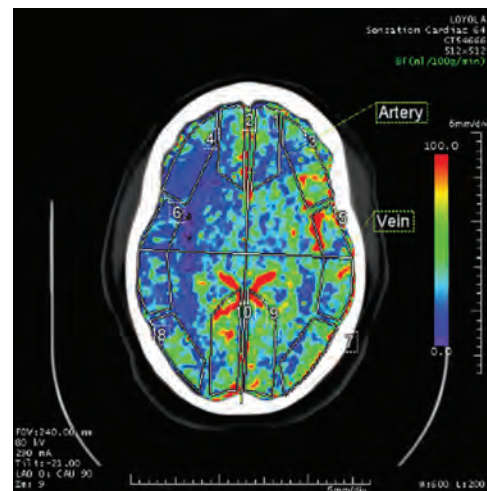


Fig. 65.26 Example of a patient with prior strokes due to a middle cerebral artery proximal stenosis, with new left-sided weakness. There is a large area of computed tomography perfusion deficit as a result of new cerebral ischemia.

of the main intracranial arteries, hemodynamic reserve assessment, and identification of high-intensity transient microembolic signals. TCD is limited in that adequate signals are available in only 80% of patients, and the technique is highly operator dependent. Therapeutic higher frequency transcranial ultrasonography simultaneous with pharmacological thrombolytic agents has been suggested to enhance clot lysis in acute ischemic stroke (Alexandrov et al., 2004). However, low frequency transcranial ultrasonography may increase the risk of hemorrhage (Daffertshofer M, et al. 2005).

Cardiac Evaluation of the Stroke Patient

Cardiac investigations to determine whether emboli have a cardiac source are advised in selected circumstances.

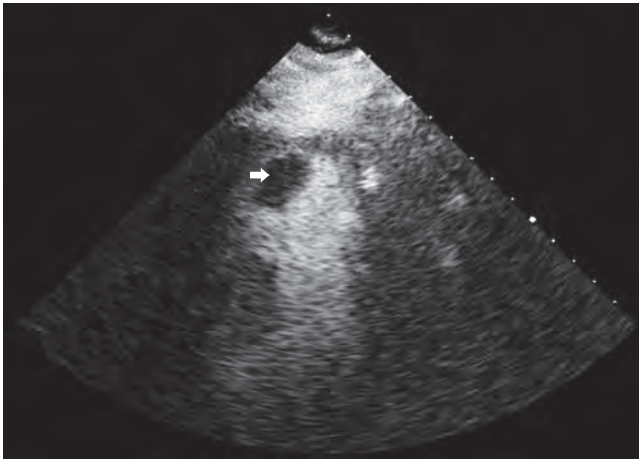


Fig. 65.27 Contrast enhanced transthoracic echocardiogram (2 chamber view) in a 62-year-old man with a left middle cerebral artery infarction showing a left ventricular apical thrombus (arrow).

Noninvasive cardiac imaging has expanded the ability to diagnose and assess a variety of cardiac conditions, many of which have been implicated as potential causes of TIA and evolving stroke. These imaging techniques differ widely in the information they provide about the morphology, function, and metabolic status of the heart. Most institutions currently use two-dimensional echocardiography to detect left ventricular thrombus with injection of agitated saline or other contrast agents to screen for right-to-left cardiac shunts. A transthoracic or transesophageal approach can be used. The morphology of the thrombus predicts its embolic potential; left ventricular thrombi that have a protruding and mobile appearance on echocardiography are most likely to embolize. The sensitivity of transthoracic two-dimensional echocardiography (TTE) in detecting left ventricular thrombi varies from 77% to 92%, specificity varies from 84% to 94%, and predictive accuracy is 79% (see Fig. 65.27).

Patients with atrial fibrillation are likely to develop atrial thrombi secondary to stasis of blood in the left atrium or left atrial appendage. Atrial thrombi are not always well visualized with routine studies. The left atrium, particularly the left atrial appendage, is often difficult to visualize with M-mode echocardiography. Left atrial thrombi can be detected successfully with TTE, but sensitivity and specificity of this technique are difficult to ascertain due to the distance between the left atrial appendage and chest wall. Transesophageal echocardiography (TEE) remains the gold standard for identifying cardiac sources of emboli. TEE is also the gold standard for detecting complex aortic plaques as a source of embolism. Because it is somewhat invasive, TEE is used in selected individuals, particularly when the transthoracic images are technically inadequate for the evaluation of mitral and aortic prosthetic valves or vegetations, whenever there is a need for better visualization of the left atrial appendage or interatrial septum, or when a right-to-left shunt, left atrial spontaneous contrast, or aortic atherosclerosis is suspected. Two-phase 64-slice (or greater) cardiac CTA is also a useful noninvasive modality for detecting high-risk cardiac sources of embolism and differentiating thrombus from circulatory stasis in stroke patients (Hur et al., 2009a, b). Continuous ECG monitoring is routinely recommended. Routine cardiac telemetry in the acute stroke period may reveal unexpected paroxysmal disturbances of cardiac rhythm, often resulting in treatment modifications, and has become a crucial element of most acute stroke units. Prolonged arrhythmia monitoring beyond the



Fig. 65.28 A 43-year-old woman with a history of hypertension, hypercholesterolemia, and tobacco use had right-sided hemiparesis. Cerebral angiogram demonstrates an occlusion of the left internal carotid artery just past the bifurcation. There is partial reconstitution via ethmoid collaterals.

acute hospital period may be useful in selected patients to detect paroxysmal atrial fibrillation.

Cerebral Angiography

Most patients with TIAs or evolving stroke have cerebrovascular atherosclerosis. The gold standard for establishing the extent of vascular disease remains conventional angiography or intra-arterial digital subtraction angiography. Either method can accurately determine the size and location of atherosclerotic lesions and aid in reliably assessing the vasculature, detecting tandem arterial lesions and the collateral circulation.

Cervicocerebral catheter-based angiography is not without complications, and its use is being challenged by the increasingly improving quality of MRA and CTA. A main disadvantage of MRA is that it overestimates the degree of stenosis related to disturbed signal from turbulent flow. Although the risks associated with cerebral angiography have been gradually decreasing, the risk for any complication is approximately 1% to 5%, of which half are minor groin hematomas. The risk for permanent neurological disability is approximately 0.2%, and the risk for death has been estimated to be 0.05%. CTA has become another useful alternative for visualization of the intracranial and extracranial arteries and has replaced conventional catheter angiography for many patients.

Catheter-based conventional cerebral angiography is still indicated in several circumstances, particularly when the diagnosis remains uncertain. It remains the foundation for safe, successful cerebrovascular interventions including administration of intra-arterial thrombolysis for ischemic stroke therapy, and extracranial and intracranial angioplasty and stenting. When a patient's evaluation fails to confirm the diagnosis, angiography may be recommended to differentiate between atherosclerotic cerebrovascular occlusive disease and nonatherosclerotic vasculopathies such as FMD, cervicocephalic arterial dissections, vasculitis, and moyamoya disease, as well as intracranial aneurysms or vascular malformations (Fig. 65.28).

Currently, angiography is seldom indicated when surgical treatment is planned; many physicians rely on multimodality noninvasive intracranial and extracranial imaging (CTA ± MRA ± carotid ultrasound) for preoperative assessment of carotid endarterectomy candidates. Angiography may still be

indicated when distinctions affecting treatment are unclear; for example, angiography can assist in cases in which differentiation between carotid and vertebrobasilar TIA or evolving stroke is uncertain on clinical grounds and noninvasive imaging only.

PREVENTING STROKE RECURRENCE: MEDICAL THERAPY

At present, general measures including control of associated risk factors such as hypertension, hyperlipidemia, cigarette smoking, as well as the use of antithrombotic agents (platelet antiaggregants and anticoagulants), antihypertensive agents, and statin therapy, remain the mainstays of medical therapy for stroke prevention. A large proportion of strokes should be preventable by controlling blood pressure, treating atrial fibrillation, and stopping cigarette smoking.

Platelet Antiaggregants

Evidence from several clinical studies favors the use of platelet antiaggregants as the first line of therapy in patients at high risk for stroke (*Antithrombotic Trialists' Collaboration, 2002; Hankey, 2004*). These agents are indicated for secondary prevention of stroke. Results of primary prevention trials do not support the use of aspirin for primary stroke prevention in low-risk, middle-aged people (*Hebert et al., 2000*). However, aspirin (81 mg) every other day was effective in primary prevention of stroke in older women. Although aspirin did not offer a long-term protective effect among 372 asymptomatic patients with carotid bruits and greater than 50% carotid stenosis on duplex ultrasonography, many physicians continue its use in patients with carotid bruits or asymptomatic carotid stenosis under the assumption that it may be effective. Data regarding intraplaque hemorrhage caused by platelet antiaggregants are conflicting.

Aspirin, the oldest and most commonly used nonprescription drug in the world, is the standard medical therapy for preventing stroke in patients with transient cerebral ischemia and for reducing the risk for recurrent stroke and postoperative strokes after carotid endarterectomy. Aspirin is effective, inexpensive, and safe if started within 48 hours of acute ischemic stroke (*Chinese Acute Stroke Trial, 1997; International Stroke Trial Collaborative Group, 1997*). Meta-analyses have shown that aspirin reduces the combined relative risk for stroke, MI, and vascular death by approximately 25%. The optimal dose of aspirin remains uncertain. Higher doses confer more gastrointestinal side effects. The recommended range of daily doses is between 50 and 325 mg of aspirin. There is a suggestion that aspirin is also effective in doses as low as 30 mg daily.

The mechanism of action of aspirin is the irreversible inhibition of platelet function by inactivation of cyclo-oxygenase (COX). Aspirin is a nonselective inhibitor of COX and is therefore able to inhibit both isoforms (COX-1 and COX-2). The antiaggregant effect is seen within 1 hour after administration. Aspirin is also anti-inflammatory, antioxidant, and may increase fibrinolytic activity up to 4 hours after administration. The main side effect of aspirin is gastric discomfort. Gastrointestinal hemorrhage occurs in 1% to 5% of cases.

In the Aspirin in Carotid Endarterectomy (ACE) trial, 2849 patients who were scheduled for CEA were randomly assigned to compare the benefits of low-dose aspirin (81–325 mg daily) with high-dose aspirin (650 or 1300 mg daily). The primary endpoints in the ACE trial were stroke, MI, or death. At 3 months after surgery, the risk for stroke, MI, or death was 6.2% in the low-dose aspirin group, compared with 8.4% in the high-dose aspirin group. The difference was less apparent

when only stroke or death was evaluated as the endpoint (*Taylor et al., 1999*). This was not a study of secondary stroke prevention, however, but a study of perioperative risk reduction in patients with asymptomatic or symptomatic carotid artery stenosis.

Ticlopidine and clopidogrel are structurally related thienopyridines that have antiplatelet effects. Ticlopidine reduces the relative risk for death or nonfatal stroke by 12% in comparison with aspirin. Ticlopidine acts primarily by irreversibly inhibiting the adenosine 51 diphosphate pathways of the platelet membrane. It also reduces plasma fibrinogen levels and increases erythrocyte deformability. The recommended dosage of ticlopidine in most of the world is 250 mg twice a day. Ticlopidine has more side effects than aspirin, including diarrhea, nausea, dyspepsia, and rash. These side effects tend to occur during the first few months of therapy. The dosage can be temporarily reduced to lessen the side effects for a few weeks then brought back to 250 mg twice a day administered with food. A more worrisome adverse reaction is reversible neutropenia, which occurs in 2.4% of cases and is severe in 0.85%. This reaction can be encountered during the first 3 months of treatment, and for this reason, a complete blood cell count must be obtained every 2 weeks during this period. The drug must be discontinued if the neutrophil count falls below 1200/mL. Rarely, thrombocytopenia and TTP may occur. One case of TTP has been described for every 2000 to 4000 patients treated with ticlopidine, making the risk for TTP with this drug among the highest reported. A post hoc analysis suggested ticlopidine was associated with increased benefit for nonwhites, women, patients with vertebrobasilar ischemia, patients whose initial event occurred on other antithrombotic agents such as aspirin, and patients without high-grade carotid artery stenosis, but data from the African American Antiplatelet Stroke Prevention Study (AAASPS) have called into question the overall benefit of ticlopidine. In the AAASPS, aspirin (650 mg daily) had fewer side effects compared to ticlopidine, and a trend toward benefit of aspirin was actually seen (*Gorelick et al., 2003*).

The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events study assessed the relative efficacy of clopidogrel (75 mg daily) and aspirin (325 mg daily) in reducing the risk of ischemic stroke, MI, and vascular death in patients with previous ischemic stroke, MI, or symptomatic atherosclerotic peripheral arterial disease. The results of this study showed that clopidogrel was modestly more effective (8.7% RRR) than aspirin. Clopidogrel is a platelet adenosine diphosphate receptor antagonist. Overall, the tolerability of clopidogrel was excellent, with no increased incidence of neutropenia and a lower incidence of gastrointestinal hemorrhage and peptic, gastric, or duodenal ulcers when compared with aspirin.

Bennett et al. (2000) studied the association of clopidogrel with TTP in 11 patients. In the majority of patients, clopidogrel had been used for less than 14 days before the onset of TTP. Several patients were taking concomitant medications, including statins in five patients, atenolol in three patients, and cyclosporine in one patient (*Bennett et al., 2000*). The rate of diarrhea, rash, and pruritus is higher with clopidogrel than with aspirin (*Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events [CAPRIE] Steering Committee, 1996*). Subsequent data from the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study suggested that a combination of clopidogrel plus aspirin with doses ranging from 75 mg to 325 mg daily was superior to aspirin monotherapy (*Yusuf et al., 2001*). In this study of patients with acute coronary syndromes, an overall 20% RRR for stroke, MI, and vascular death was seen. For stroke alone, the RRR was 14%, but the absolute difference was only 0.2% because few strokes

occurred in this study population. However, the CURE study led to an approach whereby clopidogrel and aspirin were commonly used for any cardiovascular event, including stroke. Subsequently, the Management of Atherothrombosis with Clopidogrel in High-Risk Patients (MATCH) trial, comparing clopidogrel plus 75 mg of aspirin daily with clopidogrel monotherapy, showed a nonsignificant difference in benefit for combination therapy. The RRR for combination therapy in the MATCH trial was only 6.4% ($P = 0.244$) (Diener et al., 2004). Of great concern, combination therapy in the MATCH trial was associated with a 4.5% major and life-threatening bleeding events rate compared with 1.9% for clopidogrel monotherapy ($P < 0.0001$). Results from the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization Management and Avoidance (CHARISMA) trial confirmed that clopidogrel-based combination therapy was not superior to monotherapy for primary or secondary prevention of cardiovascular events. In this study, clopidogrel 75 mg daily plus aspirin (75–162 mg daily) was compared with aspirin alone (75–162 mg daily) in 15,603 patients (Bhatt et al., 2006). The overall RRR was a nonsignificant 7.1% ($P = 0.22$) for MI, stroke, or cardiovascular death. For the endpoint of all stroke, there was a 0.8% RRR ($P = 0.05$) with a similar but not statistically significant reduction for ischemic stroke. There was a similar risk reduction for patients with history of stroke, but again this was not statistically significant. As with the MATCH trial, patients on combination therapy in the CHARISMA trial were at greater risk for bleeding complications. A direct comparison between the CURE study and MATCH trial is difficult because the degree of hypertensive control in the MATCH trial was not specified, and there were far more hypertensives and diabetics in the MATCH trial that might potentially explain the greater number of adverse events in the latter study. A number of additional studies are underway looking at clopidogrel and aspirin poststroke. These include studies of early administration of dual therapy within 12 hours after minor stroke or TIA (POINT), a study of dual therapy versus warfarin in aortic arch atheroma following an embolic event (ARCH) was completed in 2012 and final results are awaited. A study of dual-antiplatelet therapy versus aspirin (325 mg daily) and aggressive blood pressure control versus conventional antihypertensive therapy in patients with MR-proven small-vessel ischemic disease (SPS3) demonstrated no reduction in recurrent stroke for patients treated with the combination of aspirin and clopidogrel. Dual-antiplatelet therapy patients experienced nearly twice the major hemorrhage risk and 52% higher all-cause mortality compared to those on aspirin alone (SPS3 Investigators, 2012).

Dipyridamole is a cyclic nucleotide phosphodiesterase inhibitor that increases levels of cyclic adenosine monophosphate. The European Stroke Prevention Study 2 (ESPS-2), a multicenter randomized, double-blind, factorial, placebo-controlled trial, randomized patients with stroke or TIA within the previous 3 months to treatment with aspirin alone (25 mg twice a day), modified-release dipyridamole alone (200 mg twice a day), the two agents in combination, or placebo. The ESPS-2 investigators concluded that both low-dose aspirin and high-dose dipyridamole in a modified-release form alone were superior to placebo, and that the combination was significantly superior to each drug alone. The ESPS-2 investigators reported an additive effect of the modified-release dipyridamole when prescribed with aspirin, with a remarkable 37% RRR in fatal and nonfatal stroke at 2 years. Benefit was limited to stroke prevention in patients with prior stroke or TIA. There was little effect on fatal stroke and MI. The main side effects in the ESPS-2 study were headaches and gastrointestinal distress. Headache in ESPS-2 was driven by dipyridamole, with the rate of headache in ESPS-2 being

39.3% for combination therapy, 33.8% for aspirin, 38.3% for dipyridamole, and 32.9% for placebo. The rate of dyspepsia in ESPS-2 was 18.4% for combination therapy, 18.1% for aspirin, 17.4% for dipyridamole, and 16.7% for placebo. The rate of gastrointestinal bleeding in ESPS-2 was 4.1% for combination therapy, 3.2% for aspirin, 2.2% for dipyridamole, and 2.1% for placebo. The use of low-dose aspirin did not reduce the risk for bleeding (Diener et al., 1996). The European and Australian Stroke Prevention Reversible Ischaemia Trial (ESPRIT) enrolled 2739 patients with TIA, transient monocular blindness, or minor stroke (modified Rankin <3) within 6 months of symptom onset who had a non-cardioembolic source. Mean follow-up was 3.5 years. Patients were randomized to either open-label doses of aspirin ranging from 30 to 325 mg daily (mean dose of 75 mg) or extended-release dipyridamole (200 mg) plus aspirin (ESPRIT Study Group, 2006). At the end of the study, 15.7% of persons on aspirin and 12.7% on the dipyridamole regimen had a stroke, MI, or vascular death, for a 20% RRR and 1% absolute reduction in risk annually. The ESPRIT study reported that 3.85% of patients on aspirin and 2.56% of patients on dipyridamole had a major bleeding event, but the difference was nonsignificant. An updated meta-analysis of dipyridamole in stroke patients was then performed by the ESPRIT authors based on data of six trials, including 3888 patients allocated to aspirin and dipyridamole and 3907 to aspirin alone, with the total number of outcome events at 1158. The corresponding overall risk ratio was calculated at 0.82 (95% CI, 0.74–0.91) in favor of the dipyridamole and aspirin regimen. PROFESS was a direct comparison of clopidogrel and extended-release dipyridamole plus low-dose aspirin (using a factorial design to also compare telmisartan plus any other antihypertensive drugs versus any antihypertensive regimen, excluding an angiotensin receptor blocker). The study showed no difference in recurrent stroke or a composite outcome of stroke, MI or death, but the rate of hemorrhagic complications was higher in the aspirin plus dipyridamole group (Sacco et al., 2008). Cilostazol, a phosphodiesterase inhibitor, often used for stroke prevention in Japan and other Asian countries, proved superior to aspirin in preventing recurrent strokes in patients who had noncardioembolic strokes (Shinohara, 2010). Ticagrelor is a new reversible P2Y₁₂ reversible platelet aggregation inhibitor mechanistically related to clopidogrel. It was beneficial, as compared with clopidogrel, in patients with acute coronary syndromes (ACS). Patients treated with ticagrelor were less likely to die post-ACS from vascular causes, including stroke, though there was a greater chance of non-fatal bleeding in the randomized study (Cannon et al., 2007). A clinical trial of ticagrelor in patients with stroke or TAI is currently underway.

There is no persuasive evidence from current or past trials that patients benefit from the use of sulfinpyrazone or sulocitidil. GP IIb/IIIa antagonists like abciximab (ReoPro) inhibit platelet aggregation and may have additional anticoagulant, fibrinolytic, and anti-inflammatory activities. In acute ischemic stroke, a phase III trial of abciximab in acute ischemic stroke failed to show benefit for this regimen in acute ischemic stroke (AbESTT Investigators, 2005). Long-chain polyunsaturated omega-3 fatty acids may be considered in patients unable to receive platelet antiaggregants or other antithrombotic agents.

Oral Anticoagulants

Warfarin (4-hydroxycoumarin) inhibits the synthesis of factors II, VII, IX, and X, as well as proteins C and S. Oral anticoagulation with warfarin is indicated for primary and secondary prevention of stroke in patients with NVAf. Six randomized studies evaluated the primary and secondary

prevention of stroke in patients with NVAF. Three of these studies also evaluated aspirin at daily doses of 75, 300, and 325 mg, respectively. These six studies demonstrated that the relative risk for stroke is reduced by 68% with the use of warfarin (Koefoed et al., 1997). The RRR with aspirin therapy was 21% (18%–44%) (Atrial Fibrillation Investigators, 1997). Advancing age increases the risk for major hemorrhage in patients given warfarin for stroke prevention; patients older than 75 years are at greater risk for hemorrhagic complications. However, these older patients are at significantly greater risk for ischemic stroke compared to their risk for hemorrhage, and warfarin should still be considered for these patients. Therefore, NVAF patients at high risk for stroke should be treated with dose-adjusted warfarin (INR 2.0–3.0); INR values less than 2.0 and greater than 4.0 should be avoided. Patients younger than 65 years without other risk factors can be given aspirin, 325 mg/day. Low-intensity, fixed-dose warfarin plus aspirin is inadequate for stroke prevention in high-risk patients with NVAF. There is also no evidence that newer antiplatelet therapies are substitutes for warfarin. In those patients for whom the risk of bleeding complications of warfarin are unacceptably high, the combination of clopidogrel and low-dose aspirin (75–100 mg) was shown to be superior to aspirin monotherapy, though there was a slightly greater rate of bleeding complications with the combination therapy. At a median of 3.6 years of follow-up, major vascular events had occurred in 6.8% of patients receiving clopidogrel plus aspirin, compared with 7.6% of patients receiving aspirin monotherapy (relative risk [RR], 0.89; 95% CI, 0.81–0.98). Major bleeding occurred at a rate of 2% per year for patients receiving combination therapy and 1.3% in patients receiving aspirin alone (RR, 1.57; 95% CI, 1.29–1.92) (ACTIVE Investigators 2009). Anticoagulation is also recommended for patients with atrial fibrillation and hyperthyroidism. Patients who cannot tolerate pharmacological cardioversion may benefit from electrophysiological or surgical procedures. However, cardioversion to sinus rhythm does not obviate the need for long-term anticoagulation (Sherman et al., 2005). Anticoagulant therapy has a protective effect against stroke following acute MI. To prevent arterial embolism, immediate anticoagulation with heparin is initiated, followed by oral anticoagulation for 6 months, following an anterior wall MI or an MI with apical wall motion abnormalities or left ventricular thrombus. Patients with mechanical prosthetic heart valves should receive lifelong therapy with warfarin to prolong the INR to a target of 3.5. Patients undergoing elective cardioversion for atrial fibrillation should receive anticoagulation for 3 to 4 weeks before cardioversion unless there was documented onset of atrial fibrillation less than 48 hours prior to cardioversion. Use of long-term anticoagulation in patients with left ventricular aneurysms and mural thrombi is not indicated because of the low risk for embolization. Prophylactic use of warfarin to a target INR 2.0 to 3.5 in patients with dilated cardiomyopathy did not reduce the composite endpoint of ischemic stroke, intracerebral hemorrhage or all-cause mortality compared to aspirin alone (325 mg daily) in 2305 patients with low cardiac ejection fractions followed for up to 6 years. However, a 48% reduction in the hazard for ischemic stroke (95% CI, 0.33–0.82; $P = 0.005$) in the warfarin treated patients was reported (Homma et al., 2012). There are not adequate data to support anticoagulation in patients with stroke or TIA in the context of a PFO or aortic arch atheroma (Albers et al., 2004; Messe et al., 2004). Furthermore, for those patients with non-cardioembolic infarcts, the Warfarin Aspirin Recurrent Stroke Study (WARSS), a trial of 2206 patients randomized to warfarin (INR = 1.4–2.8) or aspirin (325 mg daily), did not show additional benefit for warfarin in preventing recurrent

ischemic stroke (Mohr et al., 2001). Additionally, while warfarin was previously thought to be beneficial for symptomatic intracranial atherosclerotic vascular disease, a randomized comparison of warfarin (INR 2.0–3.0) and high-dose aspirin (1300 mg daily) failed to show superiority of either therapy for the primary endpoint of stroke or vascular death (Chimowitz et al., 2005). The 2-year event rate was 22.1% for aspirin and 21.8% for warfarin, with $P = 0.83$. While there was a statistically nonsignificant ($P = 0.29$) benefit for warfarin (event rate 17.0%) versus aspirin (event rate 21.4%) for ischemic stroke, there was a statistically significant benefit for aspirin compared to warfarin for major bleeding (3.2% aspirin; 8.3% warfarin; $P = 0.01$) and nonsignificantly fewer vascular deaths (3.2% aspirin; 5.9% warfarin; $P = 0.16$). There was also a trend for aspirin superiority over warfarin in preventing subsequent MI, but the overall event rate was low, with a log-rank $P = 0.21$.

Factor Xa antagonists and direct thrombin inhibitors show great promise as substitutes for warfarin for the prevention of stroke in patients with atrial fibrillation. Dabigatran, a reversible oral thrombin inhibitor, at a dose of 110 mg was associated with rates of stroke and systemic embolism that were similar to those associated with warfarin, as well as lower rates of major hemorrhage (Connolly et al., 2009). Dabigatran at a dose of 150 mg was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage compared with warfarin. The oral factor Xa inhibitor, rivaroxaban (20 mg daily) was shown to be noninferior to warfarin for the prevention of stroke and systemic embolism in 14,264 patients with nonvalvular atrial fibrillation. Stroke or systemic embolism rates were 1.7% per year for rivaroxaban treated patients and 2.2% per year for warfarin treated patients ($P < 0.001$ for noninferiority). Major and nonmajor bleeding events were similar for both groups although there were slightly fewer intracranial (0.2% absolute reduction, $P = 0.02$) and fatal (0.3% absolute reduction, $P = 0.003$) hemorrhages in the rivaroxaban treated patients (Patel et al., 2011). Another oral factor Xa antagonist, apixaban (5 mg twice daily) was shown to significantly reduce stroke or systemic embolism compared to aspirin (hazard ratio 0.45, 95% CI 0.32–0.62, $P < 0.001$) in 5599 patients who were deemed unsuitable for warfarin without significantly affecting rates of major bleeding, intracranial hemorrhage, or death (Connolly et al., 2011). Subsequently, Apixaban (5 mg twice daily) was reported to be superior to warfarin (hazard ratio 0.79, 95% CI 0.66–0.95, $P < 0.01$) in 18,201 patients with atrial fibrillation and one or more additional stroke risk factors. The apixaban treated group experienced significantly fewer major hemorrhages, hemorrhagic strokes, and death from all causes than the warfarin treated group (Granger et al., 2011). Edoxaban, an oral factor Xa inhibitor approved for use in Japan, was compared to warfarin in a randomized controlled trial of 21,105 patients with atrial fibrillation and CHADS2 score of 2 or greater. Edoxaban 30 mg daily and 60 mg daily were reported to be noninferior to warfarin (target INR 2–3) for preventing stroke or systemic embolism. A trend was seen for greater benefit in the group receiving the higher dose of Edoxaban. Both doses of Edoxaban were associated with fewer major bleeding events (Giugliano et al., 2013).

For atrial fibrillation patients in whom antithrombotic therapy is contraindicated, percutaneous closure of the left atrial appendage may be an alternative (Holmes et al., 2009). Moreover, a post hoc analysis of dronedarone, a novel antiarrhythmic drug, suggests a reduction of stroke risk by 34% ($P = 0.027$) among patients with nonpermanent atrial fibrillation, in addition to standard therapy including anti-thrombotics (Rother and Laufs, 2010).

TREATMENT OF ACUTE ISCHEMIC STROKE

Modern therapy for acute ischemic stroke is currently being approached in four different ways. First and most important are general measures aimed at preventing and treating complications. Second are reperfusion strategies directed at arterial recanalization. Third are cytoprotective strategies aimed at cellular and metabolic targets. The fourth approach targets inhibition of the inflammatory processes associated with cerebral ischemia. Eventually, combined therapy will be used for acute ischemic stroke treatment.

Heparins and Heparinoids

Unfractionated heparin exerts its anticoagulant effect by binding to antithrombin, whereas the anticoagulant effect of LMWH is primarily mediated through the inactivation of factor Xa. Randomized studies of UFH, LMWH, or heparinoids for the treatment of acute ischemic stroke continue to show no proven benefits in the reduction of stroke-related mortality, stroke-related morbidity, early stroke recurrence, or stroke prognosis except in the case of cerebral venous thrombosis. The time window from stroke onset varied from 6 hours to 48 hours in these studies. Treatment with LMWH or heparinoids after acute ischemic stroke appears to decrease the occurrence of deep vein thrombosis compared to UFH (Sandercock et al., 2008).

Results are available from a randomized double-blind controlled trial of the LMWH, nadroparin calcium (Fraxiparine). In this trial, 312 patients were randomized within 48 hours of stroke to receive either placebo or nadroparin calcium 4100 antifactor Xa IU subcutaneously either once or twice daily. Treatment was continued for 10 days. After 10 days, all patients received aspirin, 100 mg/day. There was no difference between the groups at 3 months. However, after 6 months, there was a significant dose-dependent reduction in the rate of poor outcome among the three study groups in favor of patients treated with nadroparin calcium twice daily compared with those who received treatment once daily or placebo (Kay et al., 1995). A second randomized double-blind study involving 750 patients in 120 centers (FISS bis) failed to confirm these initial observations.

The International Stroke Trial studied approximately 20,000 patients who were randomized within 48 hours of ischemic stroke onset to receive a fixed dose of 10,000 or 25,000 units of UFH subcutaneously daily (compared with no heparin). Treatment was continued for 14 days or until hospital discharge if shorter. There was no significant difference in the rate of death or recurrent ischemic or hemorrhagic stroke at 2 weeks (11.7% with UFH and 12.0% without UFH). Patients receiving UFH had significantly fewer recurrent ischemic strokes at 2 weeks, but this was negated by a similar increase in hemorrhagic strokes (International Stroke Trial Collaborative Group, 1997).

Definite data regarding the safety and efficacy of IV heparin for acute ischemic stroke or cardioembolic stroke are lacking, but to prevent recurrence, IV heparin is sometimes given to patients with small cardioembolic infarcts associated with intracardiac thrombi diagnosed by echocardiography. In a small trial performed by the Cerebral Embolism Study Group, 45 patients with acute cardioembolic stroke who presented within 48 hours of symptom onset were randomized to receive either early or delayed treatment. The early treatment group received an IV heparin bolus of 5000 to 10,000 units followed by a maintenance infusion for at least 96 hours before the patient was switched to warfarin. Patients in the control group received no heparin and were given platelet antiaggregants or warfarin 10 days post stroke. None of the 24 patients who

received heparin experienced stroke recurrence or hemorrhage within the 96-hour treatment period. Of the 21 patients who received delayed anticoagulation, two experienced early recurrent embolic cerebral infarcts, one had a deep venous thrombosis, two had hemorrhagic transformations, and three died. The study suggested that heparin might be helpful, but the study was terminated prematurely. Heparin should not be used if a patient has a septic embolus or if CT shows a hemorrhagic or large infarction. When IV heparin is given, many physicians do not use an IV bolus and aim for a target APTT of 55 to 75 seconds, or 1.5 to 2 times control.

Intravenous UFH appears to be ineffective in patients with acute partial stable stroke. A large randomized study evaluated UFH in 225 patients with noncardioembolic stroke. Patients who had progressing deficit in the first hour of observation were excluded from the study because of the prevailing belief at that time that stroke in evolution should be anticoagulated. There was no significant difference in stroke progression or death at 7 days. However, an Italian study of acute stroke patients suggested that heparin may be of benefit if given within 3 hours of symptom onset for nonlacunar stroke (Camerlingo et al., 2005).

Other LMWHs and heparinoids also remain unproven in acute ischemic stroke. The overall results of the TOAST study using danaparoid for patients with acute ischemic stroke treated within 24 hours of symptom onset showed no benefit for anticoagulation with this agent (TOAST Investigators, 1998). A subgroup post hoc analysis, however, of patients with more than 50% stenosis or ipsilateral occlusion of the internal carotid artery showed a favorable outcome for those patients given danaparoid as opposed to placebo at 7 days (53.8% favorable outcome for danaparoid versus 38% for placebo [$P = 0.023$]) and 3 months (68.3% favorable outcome for danaparoid versus 53.2% for placebo [$P = 0.021$]) (Adams et al., 1999). The current status of antithrombotic therapy of cerebral ischemia is shown in Table 65.4.

Although convincing statistical proof is still lacking, anecdotal evidence supports early initiation of IV UFH to prevent stroke recurrence in several uncommon situations. These indications include cerebral infarction in the setting of inherited or acquired hypercoagulable states, intraluminal arterial thrombus, and extracranial cervicocephalic arterial dissections. Outcome of cerebral venous thrombosis is also improved with heparin therapy, with improvement beginning early in the course of therapy.

Thrombolytic Therapy

If patients meet appropriate criteria, IV administration of recombinant tissue plasminogen activator (rtPA) remains the only proven intervention for emergency management of acute ischemic stroke and the only approved therapy for acute ischemic stroke by the FDA. A strong correlation has been shown between arterial recanalization and neurological improvement in acute cerebral ischemia. Understanding how baseline clinical, biological, and imaging variables impact outcome is critical for the subsequent management of patients with acute ischemic stroke and future acute stroke clinical trials design (Tomsick et al., 2010).

Intravenous thrombolytic therapy with rtPA (alteplase) is recommended within 4.5 hours from onset of ischemic symptoms, adhering to the eligibility criteria and therapeutic regimen provided by the National Institute of Neurological Disorders and Stroke (NINDS) and European Cooperative Acute Stroke Study III (ECASS III) (Hacke et al., 2008b; National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group, 1995). In addition to the 4.5-hour window for presentation, patients must have an unenhanced

TABLE 65.4 Current Status of Antithrombotic Therapy of Cerebral Ischemia

Therapy	Conclusion
Apixaban	Positive*
Aspirin	Positive
Dabigatran	Positive*
Edoxaban	Positive*
Clopidogrel	Positive
Ticlopidine	Positive
Slow-release dipyridamole and aspirin	Positive
Cilostazol	Positive
Rivaroxaban	Positive*
Sulfinpyrazone	Negative
Suloctidil	Negative
Glycoprotein IIb/IIIa receptor antagonists	Negative
Warfarin	Positive*
Warfarin	Negative [†]
Heparin	Negative
Fraxiparine	Negative
Dalteparin	Negative
Certoparin	Negative
Tinzaparin	Negative
Danaparoid	Negative

*For primary and secondary prevention in patients with nonvalvular atrial fibrillation.

[†]No additional benefit in preventing recurrent ischemic stroke in patients with noncardioembolic infarcts, including patients with high-grade symptomatic intracranial stenosis.

head CT scan that does not show hemorrhage and no other contraindications to the drug. The dose of rtPA is 0.9 mg/kg, with a maximum dose of 90 mg; 10% of the total dose is given as an initial bolus, and the rest is infused over 60 minutes.

Subsequent assessment of the NINDS tPA trial using a global statistic also demonstrated a sustained benefit of IV rtPA at 6 and 12 months after the intervention in patients treated within 3 hours after onset of ischemic stroke symptoms (Kwiatkowski et al., 1999). Reanalysis of the NINDS trial was performed, and a pooled analysis of the six major rtPA acute stroke trials was also published (Hacke et al., 2004; Ingall et al., 2004). The reanalysis confirmed the previously observed benefit for tPA in the original NINDS rtPA study paper, despite apparent imbalances in baseline stroke severity; adjusted rtPA-to-placebo odds ratio of a favorable outcome was 2.1 (95% CI, 1.5–2.9). The pooled analysis confirmed that earlier treatment of stroke patients is associated with a more favorable outcome. Based on the numbers needed to treat (NNT) ratio, for every eight patients treated with tPA, one patient has excellent or complete recovery, and for every 15 patients treated, one patient has a symptomatic intracranial hemorrhage. This ratio is similar to the findings for carotid endarterectomy (CEA) for high-grade (>70%) symptomatic carotid stenosis (Schneck and Biller, 2005).

In the NINDS rtPA study, treatment did not lessen death rates or account for excess mortality. The frequency of symptomatic intracerebral hemorrhage was 10 times greater in patients given tPA (6.4% in the treatment group compared with 0.6% in the placebo group). Most hemorrhages occurred within 36 hours of treatment. Thrombolytic-related intracra-

nial hemorrhages are usually large-volume lobar bleeds, often multiple, with blood/fluid levels; intraventricular and subarachnoid extension is not uncommon. The rate of symptomatic intracranial hemorrhage in several phase IV series of rtPA in the community setting was similar to that seen in the NINDS trial (Albers et al., 2000; Chiu et al., 1998). Protocol violations have been associated with higher rates of symptomatic intracranial hemorrhages (Buchan et al., 2000; Katzan et al., 2000). Katzan and colleagues reported that in 1997–1998, fewer than 2% of all ischemic stroke patients received IV rtPA in Cleveland area hospitals. Close to 16% of those patients had a symptomatic intracranial hemorrhage, of which six were fatal. Overall, half the patients treated had deviations from national treatment guidelines. After initiation of a comprehensive stroke quality-improvement plan, however, rtPA administration rates went up dramatically, with the incidence of hemorrhage and other complications equal to that in the NINDS study (Katzan et al., 2003).

The benefits of treatment with IV rtPA also outweigh the risks among selected patients with acute ischemic stroke with symptom onset from 3 to 4.5 hours. Possible exceptions include patients older than age 80, patients with a combination of previous stroke and DM, patients on oral anticoagulants regardless of INR values, patients with NIHSS scores above 25, and patients with evidence of major infarct or CT with compromise of more than one-third of the middle cerebral artery (MCA) territory (Hacke et al., 2008a). In ECASS 3, more patients had a favorable outcome (defined as a modified Rankin scale (mRS) of 0 to 1 at 3 months) with alteplase than with placebo (52% vs 45%). An expansion of the time window to 4.5 hours has been endorsed by the American Heart Association/American Stroke Association (Del Zoppo et al., 2009) but as yet is not approved by the FDA.

Intravenous rtPA administration requires close adherence to protocol guidelines. Patient management following rtPA administration requires close neurological and blood pressure monitoring, as well as capabilities to handle potential hemorrhagic complications associated with thrombolytic therapy, by physicians experienced in the management of cerebrovascular disease. Centers that do not have these capabilities can still administer IV rtPA in partnership with tertiary care facilities by starting the drug and transferring the patient. Successful centers have treated up to 15% to 20% of ischemic strokes with thrombolytic therapy, although nationally only a few percent of patients are likely to be treated with thrombolytic therapies. Formal certification of primary stroke centers commenced in 2003. A model that mirrors the trauma system with primary and comprehensive designated stroke centers has evolved in the United States with the formal certification of comprehensive stroke centers in 2012 (Albers et al., 2000, 2005).

Inclusion criteria for administration of rtPA in the NINDS rtPA trial were acute ischemic stroke with a clearly defined time of onset (< 3 hours), neurological deficit measurable on the NIH Stroke Scale, and CT scan without evidence of intracranial hemorrhage. Patients who awoke from sleep had symptom onset defined as “when last seen awake and normal.” Exclusion criteria for administration of rtPA were rapidly improving or isolated minor neurological deficits, seizure at the onset of stroke, prior intracranial hemorrhage, symptoms suggestive of subarachnoid hemorrhage, blood glucose less than 50 mg/dL (2.8 mmol/L) or greater than 400 mg/dL (22.2 mmol/L), gastrointestinal or genitourinary bleeding within the 3 weeks before stroke, recent MI, current use of oral anticoagulants (PT > 15 seconds or INR > 1.7), a prolonged aPTT or use of heparin in the previous 48 hours, platelet count less than 100,000/mL, another stroke or serious head injury in the previous 3 months, major surgery within the previous 14 days, arterial puncture at a noncompressible site within the

previous 7 days, or pretreatment SBP 185 mm Hg or higher or DBP 110 mm Hg or higher. Some of these original exclusion criteria were subsequently modified. In particular, seizure at onset of symptoms is considered an exclusion only if residual impairments are postictal, and only blood glucose levels below 50 mg/dL are an exclusion without an upper value as previously recommended (Jauch et al., 2013). More recently, recent MI, gastrointestinal or genitourinary bleeding, and recent surgery have become relative contraindications and it may be reasonable to treat selected patients with these factors (Jauch et al., 2013).

The use of IV rtPA in the ATLANTIS trial was terminated early because of nonstatistical efficacy at interim analysis (Clark et al., 1999). Favorable outcome at 3 months was 42.3% for those treated with tPA, versus 38.9% for those treated with placebo. Mortality at 3 months was 11.0% for tPA-treated patients versus 6.9% for those patients receiving placebo. Symptomatic intracranial hemorrhage occurred in 7.0% of tPA-treated patients. The Second European-Australasian Acute Stroke Study investigators assessed the safety and efficacy of IV alteplase (0.9 mg/kg of body weight) administered within 6 hours of ischemic stroke onset and failed to confirm a statistical benefit for alteplase; symptomatic intracranial hemorrhage occurred in 8.8% of alteplase-treated patients and in 3.4% of placebo-treated patients (Hacke et al., 2008b). An earlier study using a dose of tPA of 1.1 mg/kg also failed to demonstrate therapeutic efficacy among 620 patients treated within 6 hours from ischemic stroke onset (Hacke et al., 1995). Favorable outcome at 3 months was 35.7% for those treated with tPA versus 24.3% for those receiving placebo. Mortality at 3 months was 22.4% for rtPA-treated patients versus 15.8% for those treated with placebo (Clark et al., 1999; Hacke et al., 1998).

Despite consistently lower frequency of intracerebral hemorrhage with the use of streptokinase rather than tPA in patients with acute MI, current data do not support the use of IV streptokinase (1.5 million units) in acute ischemic stroke.

The following seem to be predictors of favorable outcome with IV thrombolytic therapy with tPA for acute ischemic stroke: treatment within 90 minutes of symptom onset, normal baseline CT scan, milder baseline stroke severity, no history of DM, normal pretreatment blood glucose level, and normal pretreatment blood pressure. The following seem to portend a less favorable outcome and/or increased risk for cerebral hemorrhage: extended area of low attenuation with mass effect or low attenuation on a third or more of the MCA territory on pretreatment CT scan; advanced age; prior head injury; DM; marked elevation of the blood pressure before, during, and after treatment; hypertension requiring postrandomization antihypertensive treatment; severe pretreatment neurological deficits; and protocol violations according to the NINDS study protocol (Hacke et al., 2004). Overall, for every 100 patients with acute ischemic stroke treated with IV tPA in the 0- to 3-hour window, 32 patients benefit and three patients are harmed. For every 100 patients with acute ischemic stroke treated with IV tPA in the 3- to 4.5-hour window, 16 patients benefit and three are harmed (Fig. 65.29).

A number of other thrombolytic drugs have been investigated. Tenecteplase (TNK) is a thrombolytic agent with a longer half-life, improved fibrin specificity, and increased resistance to plasminogen activator inhibitor 1 (PAI-1) compared to tPA (Haley et al., 2005). A small phase IIb dose-finding study of TNK in 75 patients randomized to TNK 0.1 mg/kg, TNK 0.25 mg/kg, or alteplase 0.9 mg/kg reported significantly favorable imaging and clinical outcomes for patients receiving the higher TNK dose without a significant impact on intracranial bleeding risk (Parsons et al., 2012). Desmoteplase is a genetically engineered version of a clot-dissolving protein from vampire bats. The Desmoteplase in

Acute Ischemic Stroke (DIAS) study and the Dose Escalation Study of Desmoteplase in Acute Ischemic Stroke (DEDAS) were randomized phase II clinical trials of patients who were enrolled within 3 to 9 hours of symptom onset using MRI criteria to identify those eligible for the trials on the basis of diffusion/perfusion mismatch. DEDAS demonstrated clinical improvement of up to 60% compared with placebo in patients who received a dose of 125 mg/kg. The hemorrhage rate was relatively low, around 2% of patients. The DIAS study showed similar results (Hacke et al., 2005). A phase III Desmoteplase in Acute Stroke Trial 2 (DIAS-2) was negative. However, the DIAS-3 and DIAS-4 studies for patients with acute ischemic stroke onset from 3 to 9 hours, and proximal cerebral artery occlusion, are ongoing (von Kummer et al., 2012).

Abciximab is a chimeric mouse/human monoclonal antibody with high binding for the platelet glycoprotein IIb/IIIa receptor. In a phase II safety study enrolling 400 patients within 6 hours of ischemic stroke, there was a low rate of symptomatic intracranial hemorrhage (3.6% of patients treated with drug [7/195] vs 1% for placebo [2/199]) (AbESTT Investigators, 2005). However, a subsequent phase III trial was stopped because of lack of benefit.

Argatroban is a direct IV thrombin inhibitor that was studied in a randomized double-blind placebo-controlled safety study of two doses in patients with acute stroke (<12 hours from symptom onset); there was no increase in hemorrhagic complications between a low- and high-dose regimen. However, the study was not powered to assess efficacy of this agent (LaMonte et al., 2004).

Certain patients deemed unsuitable for IV thrombolytic therapy may be candidates for intra-arterial fibrinolysis. This may be considered within the first 6 hours (or longer in cases of basilar artery occlusive disease) after the onset of symptoms at hospitals with appropriate facilities. Recombinant prourokinase (r-pro-UK) was tested in the Prourokinase in Acute Cerebral Thromboembolism (PROACT) II trial. In this multicenter phase III randomized controlled trial, 180 patients with angiographically proven occlusion of the MCA (M1 or M2 occlusion) were given local intra-arterial pro-UK within 6 hours of symptom onset. Of the treated patients, 40% were functionally independent (compared with 25% of the placebo group patients) 3 months after treatment ($P = 0.04$). The efficacy of treatment seemed to fall off after approximately 5 hours. Treated patients, however, also encountered a higher risk for intracranial hemorrhage with neurological deterioration within 24 hours of treatment (10% vs 2% in the control group; $P = 0.06$) (Furlan et al., 1999). While pro-UK was not approved by the FDA, the off-label use of intra-arterial tPA has become widely used within the interventional stroke realm (Ng et al., 2004). In general, poor outcome factors for acute intra-arterial thrombolysis include older age, coma and quadriplegia at presentation, thrombotic (as opposed to embolic) occlusions, longer occlusions with poor collaterals, bilateral vertebral artery and caudal basilar artery occlusions, and failure to recanalize occluded arteries. Furthermore, it is currently unclear which thrombolytic drug and what doses to use; the type, amount, and timing of antithrombotic strategies to use afterward; and the relationship of outcome to time to treatment. There may also be a longer time window for treatment for the vertebrobasilar as opposed to carotid circulation.

Mechanical thrombectomy with newer catheter techniques has also been actively explored because of the hemorrhagic risks associated with various drugs. A number of devices have been tested for patients who are not within the time window or are not eligible for IV tPA (e.g., recent surgery).



The MERCI coil retriever catheter was approved for retrieval of cerebral “clots.” The device is used in many patients for whom IV tPA is not an option (Smith et al., 2005). The MERCI study demonstrated a recanalization rate in 46% (69/151) of patients in a single-arm study that used the placebo historical control group of the PROACT-II study as a comparator. In the PROACT-II control group, 18% of patients achieved the recanalization rate. There was symptomatic intracranial hemorrhage in 7.8% of the MERCI cases. Mortality occurred in 32% of recanalized patients versus 54% of unrecovered patients ($P = 0.01$), with a good outcome (Rankin <2) in 46% of recanalized patients compared with only 10% of unrecovered patients ($P < 0.001$). By contrast, however, there was a 27% mortality rate in the placebo control arm of the PROACT-II study, and the MCA recanalization rate of 45% in the MERCI trial compared unfavorably with the 66% recanalization rate in the pro-UK arm of the PROACT-II study (Becker and Brott, 2005). Newer-generation coil retrievers within 8 hours of symptom onset have been associated with higher recanalization rates when compared to first-generation devices, but these differences did not reach statistical significance (Smith et al., 2008). Further advances in thrombectomy technology such as aspiration catheters and stent retrievers have continued to improve recanalization rates with acceptable complication rates (Nogueira et al., 2012; Penumbra Pivotal Stroke Trial Investigators, 2009; Saver, 2012). Although newer generation thrombectomy devices have demonstrated improved neurological outcomes compared to coil retrievers, initial randomized clinical outcome data did not support thrombectomy devices compared to standard therapy using concurrent controls. A randomized study of 362 patients with ischemic stroke onset within 4.5 hours demonstrated no difference in 3-month outcome between patients receiving an endovascular recanalization

strategy (IA rtPA with or without thrombectomy) and those receiving IV rt-PA. However, the median time to treatment was 1 hour shorter for those receiving IV rt-PA and a thrombectomy device was utilized in only a third of patients that received endovascular treatment (Ciccione et al., 2013). The Interventional Management of Stroke (IMS) III trial investigated a strategy of endovascular rescue therapy in patients who had received IV-rt-PA within 3 hours of ischemic stroke onset. Although symptomatic intracerebral hemorrhage rates were similar between the group receiving IV rt-PA followed by endovascular therapy (6.2%) and those receiving IV rt-PA therapy alone (5.9%), the study was stopped early after 656 patients had been randomized as no improvement in favorable 90-day clinical outcome (mRS 0–2) was observed. Thrombectomy catheters were employed in 54% of patients in the endovascular therapy group. Stent retrievers became available toward the end of the trial and were used in only five patients. Predefined subgroup analyses suggested a possible favorable effect for patients treated with endovascular therapy within 90 minutes of IV rt-PA initiation and that received IV rt-PA within 2 hours of symptom onset (Broderick et al., 2013).

Many centers use penumbral imaging criteria to select patients with ischemic stroke who may benefit from endovascular therapy. The Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) study randomized 118 ischemic stroke patients with demonstrable large vessel, anterior circulation occlusion to thrombectomy or standard care within 8 hours of symptom onset. Patients received pre-treatment penumbral imaging with a CT or MRI-based protocol. Patients with a favorable penumbral pattern did not achieve improved clinical outcomes at 90 days when treated with thrombectomy than did those treated with standard care (Kidwell et al., 2013).

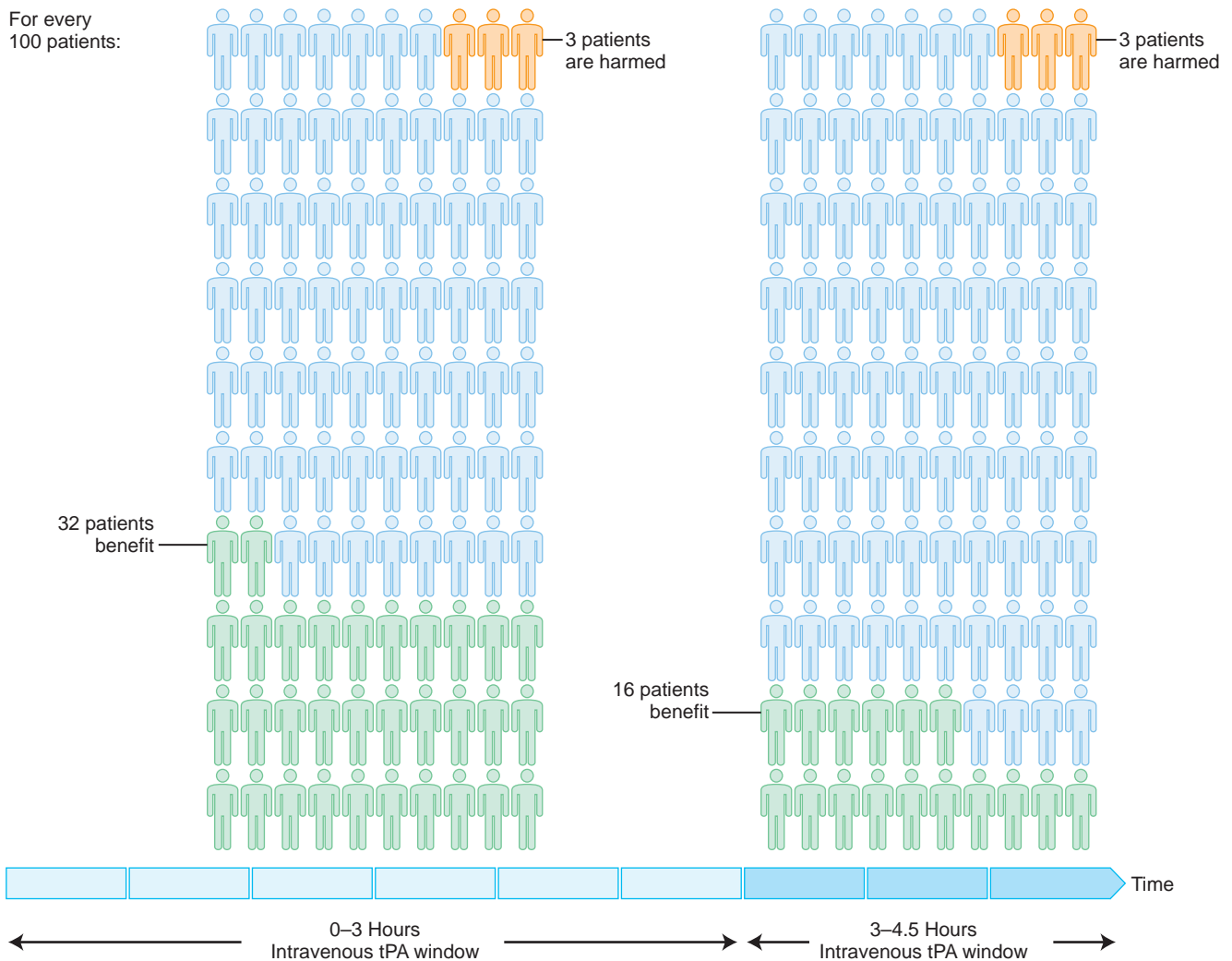


Fig. 65.29 Risk/benefit ratio of intravenous tissue plasminogen activator (tPA) for acute ischemic stroke in the 0- to 3-hour and 3- to 4.5-hour windows. (Created and designed by Gabriel A. Biller.)

More recently, several thrombectomy trials have reported clinical benefits using newer generation devices. The Multi-center Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) randomized 500 adult patients with ischemic stroke within 6 hours of onset, an NIHSS 2 or greater and an established proximal vessel occlusion in the anterior circulation, to standard care including IV rt-PA when appropriate or standard care plus endovascular treatment. Stent retrievers were employed in 81.5% of the endovascular group. IV rt-PA was given in 87% of patients randomized to endovascular therapy and 91% of control patients. The adjusted common odds ratio for an improvement in mRS at 90 days was 1.67 favoring intervention. At 90 days, mRS of 0–2 was achieved in 33% of the endovascular group compared to 19% of control patients. Mortality and serious adverse events including symptomatic intracerebral hemorrhage, were similar between the groups (Berkhemer et al., 2015).

The Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE) trial was terminated after an interim analysis of the initial 315 randomized patients demonstrated efficacy. Eligible patients were 18 years or older with a disabling ischemic stroke within 12 hours of onset. Additionally, patients had to have CT angiography evidence of

proximal occlusion of the distal internal carotid artery, or M1 or M2 segment of the middle cerebral artery, and good to moderate collateral filling by multiphase CT angiography. IV rt-PA was used in 73% of patients in the intervention group and 79% of control patients. Only 15.5% of patients were randomized beyond 6 hours of onset. The median stroke onset to reperfusion was 241 minutes. The adjusted common odds ratio for an improvement in mRS at 90 days was 3.1 in favor of intervention. A favorable outcome (mRS 0–2) at 90 days was achieved in 53% of patients in the interventional group compared to 29.3% of control patients. Mortality in the interventional group was half that of the control group and the symptomatic intracerebral hemorrhage rates were comparable (Goyal et al., 2015).

The Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial (EXTEND-IA) trial was also halted early after the initial 70 patients had been randomized to either intervention (groin puncture within 6 hours of stroke onset) or standard care. Eligible patients had to have an ischemic stroke within 4.5 hours of onset, evidence of distal internal carotid artery or middle cerebral artery stem occlusion, and received IV rt-PA. Imaging eligibility requirements included an infarct core less than 70 mL and ischemic penumbra greater than 10 mL. Median time from stroke onset to initial recanalization was 248 minutes and reperfusion was

TABLE 65.5 Randomized Clinical Trials of Mechanical Thrombectomy for Acute Ischemic Stroke

	MR CLEAN	SWIFT PRIME	EXTEND-IA	ESCAPE
Number of patients	500	196	70	316
IV rt-PA rate intervention vs control	87% vs 91%	100% vs 100%	100% vs 100%	73% vs 79%
Imaging	CT/CTA	CT/CTA or MRA	CT/CTA/CTP	CT/multiphase CTA
Target vessels	ICA, M1, M2, A1, A2	ICA, M1	ICA, M1, M2	ICA, M1, M2
NNT to achieve mRS 0–2 at 90 days	7.4	4.3	3.2	4.2
Median onset to groin puncture (minutes)	260	252	210	185
Treatment group sICH rate	7.7%	1%	0%	3.6%
Comments		NIHSS improvement by 4.6 points at 27 hours	Lower mortality and improved 24 hour NIHSS	

CT, computed tomography; *CTA*, computed tomographic angiogram; *MRA*, magnetic resonance angiography; *ICA*, internal carotid artery; *IV rt-PA*, intravenous recombinant tissue plasminogen activator; *M1*, middle cerebral artery first segment; *M2*, middle cerebral artery division; *sICH*, symptomatic intracerebral hemorrhage; *mRS*, modified Rankin scale; *NIHSS*, National Institute of Health Stroke Scale; *NNT*, number needed to treat.

achieved in 100% of the patients in the endovascular group compared to 37% of control patients ($P < 0.001$). By 24 hours, 80% of patients in the endovascular group had improved by 8 or more points on the NIHSS, compared to 37% in the control group ($P = 0.002$). Independent outcome (mRS 0–2) at 90 days was achieved in 71% of the endovascular treatment group and 40% of the control group ($P < 0.01$). There were no significant differences in mortality or symptomatic intracerebral hemorrhage between groups (Campbell et al., 2015).

The Solitaire FR With Intent For Primary Endovascular Treatment for Acute Ischemic Stroke (SWIFT PRIME) trial was also halted after 196 patients had been randomized. Patients 18–80 years old with NIHSS 8–29 and occlusion of the distal internal carotid artery or middle cerebral artery stem were randomized to thrombectomy with a stent retriever (groin puncture within 6 hours of stroke onset) or control. Eligible patients had to present within 4.5 hours and received IV rt-PA. Functional independence (mRS 0–2) at 90 days was achieved in 60% of the intervention group and 36% of the control group ($P = 0.008$). Mean NIHSS at 27 hours was also significantly lower in the intervention group. Mortality, serious adverse events and symptomatic intracerebral hemorrhage rates were similar between the groups (Table 65.5).

An extended version of this section is available at <http://www.expertconsult.com>.

Defibrinogenating and Hemorheological Agents

Ancred, an enzyme extracted from the venom of the Malayan pit viper, lowers fibrinogen and blood viscosity, inhibits erythrocyte aggregation, indirectly stimulates thrombolysis, and possibly causes local vasodilatation. It also has a weak anticoagulant effect at high dosages.

Its potential as a treatment for ischemic stroke was shown to be beneficial when initiated within 3 hours of stroke onset in the multicenter Stroke Treatment with Ancred Trial (Sherman et al., 2000). The positive results of this study were not replicated in a subsequent study of IV ancred within 6 hours after stroke onset (Levy and del Zoppo, 2009). Hemorheological therapy with isovolemic, hypovolemic, or hypervolemic hemodilution has been ineffective in the past. A study of high-dose human albumin (2 g/kg 25% albumin)

administered within 5 hours of ischemic stroke showed no benefit (90-day mRS 0 or 1) compared to an equivalent volume of isotonic saline (Ginsberg et al., 2013).

Neuroprotective Agents

Despite widespread interest in neuroprotective drug therapy and positive results in experimental animals, no neuroprotective agent has been approved to date by the FDA for acute ischemic stroke (O'Collins et al., 2006).

An extended version of this section, as well as the topic of hypothermia, can be found at <http://www.expertconsult.com>.

Surgical Therapy

Symptomatic Carotid Artery Stenosis

Stroke is often caused by atherosclerotic lesions of the carotid artery bifurcation; approximately 15% of ischemic strokes are due to extracranial internal carotid artery stenosis. Carotid atherosclerosis develops in areas of low vessel-wall shear stress, most commonly the carotid bulb. In addition to the degree of carotid artery stenosis, plaque structure has been postulated as a critical factor in defining stroke risk. Ulcers found during CEA have been associated with cerebral artery microemboli detected by transcranial Doppler. Echolucent carotid artery plaques may also be associated with an increased risk for stroke. CEA, by removing the atherosclerotic plaque, restores cerebral blood flow and reduces the risk for cerebral ischemia. Results from three major prospective contemporary studies provide compelling evidence of the benefit of CEA performed by experienced surgeons in improving the chance of stroke-free survival in high-risk symptomatic patients. Timely surgical intervention in selected patients with hemispheric TIAs, amaurosis fugax, or completed nondisabling carotid territory strokes within the previous 6 months, and with 70% to 99% diameter-reducing carotid stenosis, can significantly reduce the risk for recurrent cerebral ischemia or death. Other factors that increase the risk for ipsilateral stroke are hemispheric (rather than retinal) site of ischemia, ulcerative nature of the stenosis, presence of contralateral carotid artery occlusion, and vascular risk factors. Benefits of CEA are similar for men and women for high-grade carotid stenosis,

More than 120 controlled clinical trials involving more than 21,000 subjects and investigating numerous neuroprotective interventions have yielded negative results (Ginsberg, 2008). Unfortunately, very few of these studies included patients within the first 4 to 6 hours of ischemia. New agents (intrathecal agents, oxygenated fluorocarbon nutrient emulsions, α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid antagonists, potassium channel openers, minocycline, and high-dose statins) have been proposed. Intracellular adhesion molecules (ICAMs) are molecules to which leukocytes adhere and which facilitate migration of leukocytes through the endothelium. Some of these molecules are expressed in the cerebral vasculature during ischemia. Neutrophils in particular can contribute to tissue injury by obstructing capillaries and possibly by liberating cytotoxic products. Prevention of neutrophil adhesion by infusion of monoclonal antibodies directed at ICAMs improved neurological outcome in animal models of transient ischemia, but clinical trials yielded negative results. The sudden decrease in blood flow after ischemia provokes a cascade of events eventually leading to cell death. These events include the release of excitatory amino acids (EAAs) with secondary opening of ion channels, which leads to an increase in intracellular calcium concentration, activation of enzymes, and generation of free radicals. Several agents have been shown *in vitro* and in animal studies to interfere at various steps of this cascade, thus potentially protecting the cells from ischemia. Cerebroselective calcium channel blockers such as nimodipine have been tested in acute stroke, but the benefits for patients with acute ischemic stroke remain unproven. Endogenous EAA neurotransmitters play a major role in the pathogenesis of cerebral ischemia. In animals, EAA antagonists reduce the size of an infarct after occlusion of a major artery. From preliminary studies, some of these compounds appear to be safe in humans, but their efficacy has not been demonstrated, and several clinical trials yielded negative results. Optimal protective regimens may necessitate blocking of both *N*-methyl-d-aspartate (NMDA) and nonNMDA receptors. Pre-hospital administration of magnesium, an NMDA antagonist, to patients with suspected stroke was reported to be safe but did not improve clinical outcomes in a randomized controlled trial (J. Saver, personal communication, International Stroke Conference, San Diego, CA, February 13, 2014). Free radicals produced during ischemia can degrade polyunsaturated lipids, which are building blocks of cellular membranes, by means of lipid peroxidation. The CNS appears particularly susceptible to free radical injury. The 21 aminosteroid compounds inhibit lipid peroxidation by scavenging free radicals. Tirilazad is one such compound that decreases damage secondary to global ischemia in experimental animal models, but its clinical application in the treatment of patients with ischemic stroke has not been established.

Cerovive (NXY-059), a free radical trapping agent, administered within 6 hours of symptom onset was associated with improvement in primary outcome of disability post stroke ($P = 0.038$) by the modified Rankin scale (mRS) in the SAINT I study of 1722 patients (Lees et al., 2006). This randomized double-blind placebo-controlled study reported a favorable outcome regardless of stroke severity, with an odds ratio of 1.2. The Barthel Index supported the primary mRS findings. However, no statistical difference of clinical deficits, as measured by the National Institutes of Health Stroke Scale (NIHSS) scores, was seen in this trial. Safety of this drug was comparable with placebo, and there was also a suggestion of less intracranial hemorrhage in patients who received the study drug along with tPA. A subsequent study showed no effect of treatment versus placebo in patients with acute ischemic stroke (Diener et al., 2008). Neurotrophins are factors known to promote cell growth in certain neuronal populations. Studies have shown that some of these factors given intraventricularly to animals during ischemia reduce infarct size. The mechanism of action is still unknown but could be related to interaction with EAAs. Calpains are cytosomal enzymes that are normally quiescent but become activated by increases in intracellular calcium concentration. These enzymes have many proteins as their targets, and thus their activation can cause considerable damage. In experimental models of stroke in animals, intra-arterial infusion of calpain inhibitors given after onset of ischemia significantly reduced infarct size compared with controls. The value of calpain inhibitors in humans has not been established. Treatments with gangliosides, barbiturates, prostacyclin, opiate antagonists, aminophylline, β -adrenergic receptor blockers, vasopressor therapy, naftidrofuryl, clomethiazole, inhibitors of leukocyte adhesion, fosphenytoin, lubeluzole, basic fibroblast growth factor, and citicoline have been ineffective.

Hypothermia

Therapeutic hypothermia is a well-established neuroprotective strategy in the management of anoxic encephalopathy after cardiac arrest and perinatal asphyxia. Fever in stroke patients is associated with poor outcomes, and induced hypothermia may be neuroprotective in patients with acute cerebral ischemia. A number of hypothermic strategies are being investigated in acute ischemic stroke, and several small clinical trials have been performed, including the combination of caffeine with hypothermia in patients with acute stroke given IV rtPA (Martin-Schild et al., 2009). While the validity of these hypothermia protocols is unproven, aggressive management of fever should be pursued in all acute stroke patients (Jauch et al., 2013).

but the benefit is less certain for moderate-grade stenosis. Older age by itself should not be considered a contraindication for properly selected patients with symptomatic high-grade carotid artery stenosis, but there are no data supporting CEA for octogenarians.

The North American Symptomatic Carotid Endarterectomy Trial (NASCET) confirmed the effectiveness of CEA for preventing stroke in 659 symptomatic patients with TIAs or minor strokes with high-grade (70%–99%) diameter-reducing carotid artery stenosis. A uniform and strict technique measured carotid artery stenosis from an arteriogram. For different endpoints, absolute risk reductions in favor of surgery were 17.0% for ipsilateral stroke; 15.0% for all strokes; 16.5% for the combined outcomes of all strokes and death; 10.6% for major ipsilateral stroke; 9.4% for all major strokes; and 10.1% for major stroke and death. Longer-term outcome was also better for surgically treated patients despite an occluded contralateral carotid artery. The European Carotid Surgery Trial (ECST) also indicated the benefit from CEA compared with medical therapy in patients with mild carotid territory ischemic events associated with a diameter-reducing proximal internal carotid stenosis between 70% and 99%. The cumulative risk for any ipsilateral stroke at 3 years was 10.3% for the surgical group and 16.8% for the medical group. The ECST used different criteria than the NASCET for measurement of carotid artery stenosis on angiography.

A diameter-reducing carotid artery stenosis of 70% to 99% by NASCET criteria is equivalent to a stenosis of 82% to 99% by ECST methodology; likewise, a stenosis of 70% to 99% by ECST criteria is equivalent to a stenosis of 50% to 99% by NASCET criteria.

These methodological differences were more important with mild carotid artery stenosis. The Veterans Administration (VAH) Trial of Carotid Endarterectomy in Symptomatic Carotid Stenosis was terminated early because of the positive results of the NASCET and ECST. The Veterans Administration study also showed that CEA improved outcome in selected symptomatic patients with high-grade extracranial carotid artery stenosis. Among symptomatic patients with less than 30% stenosis, results from the ECST favor the use of medical therapy with platelet antiaggregants.

The utility of CEA for symptomatic patients with 30% to 69% carotid artery stenosis has also been determined. Results were analyzed separately for those patients with 30% to 49% and those with 50% to 69% stenosis. Analysis from 1599 patients suggests that CEA is not indicated in most of these patients (European Carotid Surgery Trialists' Collaborative Group, 1996).

With a low surgical risk, CEA also provides modest benefit in symptomatic patients with carotid artery stenosis of 50% to 69% (Barnett et al., 1998), especially among men with hemispheric ischemia who are not diabetic. CEA provides no benefit if the stenosis is less than 50% (50% by NASCET criteria is equal to 75% stenosis by ECST criteria).

Overall for patients with 70% to 99% internal carotid artery stenosis, the absolute risk reduction with surgery, based on the 5-year risk of stroke combined data from NASCET, ECST, and VAH, was 15.6% with an RRR of 48%. This translates into a number needed to treat (NNT) of 6. Thus, 156 strokes could be prevented by 1000 carotid endarterectomies. For patients with 50% to 69% stenosis, the absolute risk reduction is 7.8%, with an RRR of 28%. This translates into an NNT of 13. Thus, 78 strokes could be prevented by 1000 carotid endarterectomies. Conversely, for patients with a "string" sign, the absolute risk reduction was 0.1%; thus no strokes are prevented with carotid endarterectomies in this subgroup of patients. The benefit of CEA is highly dependent on surgical risk. Mortality and morbidity due to CEA are significantly lower for

asymptomatic patients. The acceptable level of surgical risk varies with the indication for carotid artery surgery. Maximal acceptable limits of surgical risks for combined perioperative neurological morbidity and mortality are 3% for asymptomatic patients, 5% for patients with TIAs, 7% for patients with stroke, and 10% for patients with recurrent stenosis. A combined analysis of the NASCET and ECST also showed that men fared better than women, and patients in the seventh decade of life had equal or greater benefit compared to younger patients (Rothwell et al., 2004).

Whether selected patients should undergo CEA on the basis of duplex scanning alone (without cerebral angiography) or duplex scanning complemented by MRA or CTA remains controversial. However, early intervention following symptom onset is critical. Pooled data of the ECST and NASCET showed that time from the last symptomatic event to treatment is an important factor in modifying the benefit for CEA. As delays to CEA increased, there was a marked decline in CEA benefit. For patients with symptomatic stenosis of greater than 50% diameter, the NNT to prevent one stroke was 5 for those treated within 2 weeks of symptoms, compared to 125 for patients treated more than 12 weeks post event (Rothwell et al., 2004).

Options for intervention are limited when the carotid artery is totally occluded. An estimated 61,000 first-ever strokes and 19,000 TIAs per year may be associated with carotid occlusion. However, as opposed to coronary artery occlusions, bypass of an occluded carotid artery has not been shown to be associated with better outcome. An early randomized study of medical therapy versus extracranial/intracranial (EC/IC) bypass surgery failed to show a benefit for surgery, and the procedure was largely abandoned in the ensuing decades, with exceptions for certain unique circumstances such as moyamoya disease. The original EC/IC bypass study was widely criticized, however, because of selection biases and failure to identify a subgroup with possible hemodynamic compromise that might be more likely to benefit from the procedure. The measurement of oxygen extraction fraction (OEF) by positron emission tomography (PET) has allowed investigators to identify particular high-risk patients who might benefit from EC/IC bypass. These patients have been enrolled in the Carotid Occlusion Surgery Study (COSS) that screened patients with carotid occlusion for low OEF measured by PET; those patients were then randomized to best medical therapy or best medical therapy plus EC/IC bypass surgery. In spite of excellent graft patency, EC/IC bypass surgery was no better than best medical therapy in the secondary prevention of ischemic stroke in COSS (Powers et al., 2011).

Asymptomatic Carotid Artery Stenosis

Asymptomatic carotid artery atherosclerosis is prevalent in the general population, especially in the elderly. Compared with symptomatic stenosis, asymptomatic carotid artery stenosis is associated with a relatively low risk for ipsilateral cerebral infarction. Clagett and colleagues followed only 57 asymptomatic patients with cervical bruits and abnormal ocular pneumoplethysmography; only 29 were truly randomized to aspirin therapy or CEA. More unfavorable outcomes were noted in those patients undergoing CEA, and the researchers concluded that most asymptomatic patients with cervical bruits and abnormal ocular pneumoplethysmography are appropriately managed without CEA. The Carotid Artery Surgery Asymptomatic Narrowing Operations versus Aspirin (CASANOVA) trial enrolled asymptomatic patients with 50% to 90% carotid artery stenosis. Patients with greater than 90% carotid artery stenosis were excluded on the basis of presumed surgical benefit. Overall, the trial showed no difference

between the medically and surgically treated groups. The Mayo Asymptomatic Carotid Endarterectomy Trial was terminated early because of higher rates of MI and TIA in the surgical group. Patients in the surgical group did not receive aspirin, probably explaining those results. The Veterans Affairs Asymptomatic Carotid Endarterectomy Trial evaluated 444 asymptomatic patients with angiographically proven carotid stenosis of 50% to 99%. The study showed an RRR in the incidence of ipsilateral neurological events in favor of surgery when both TIA and stroke were included as composite endpoints. However, when ipsilateral stroke was considered alone, only a nonsignificant trend favoring surgery was noted. For the combined outcome of stroke and death, no significant differences were found between the two treatment arms. The Asymptomatic Carotid Atherosclerosis Study (ACAS) found that CEA combined with aspirin and risk factor reduction was superior to aspirin and risk factor reduction alone in preventing ipsilateral stroke in patients younger than 80 years who had greater than 60% asymptomatic carotid artery stenosis. The ACAS angiography methods were similar to those of the NASCET. All patients randomized to the surgical arm of the study had a catheter angiogram but it was not mandatory in the medically treated patients. The aggregate procedural morbidity and mortality of the ACAS participating surgeons were extremely low. Based on a 5-year projection, the ACAS showed that CEA reduced the absolute risk for stroke by 5.9% (which corresponds to an absolute risk reduction of only 1% per year), and the relative risk for stroke and death by 53%. The surgical benefit incorporated a perioperative stroke and death rate of 2.3%, including a permanent arteriography complication rate of 1.2%. It is also important to note that all patients with 60% to 99% stenosis were analyzed together in this study. Similar results have been reported from the Asymptomatic Carotid Surgery Trial (ACST), a European trial of highly selected patients with greater than 70% carotid artery stenosis (by ultrasound) and no prior history of cerebrovascular disease (Halliday et al., 2004). In the ACST, the 5-year stroke risk for surgery was 6.4% compared with 11.8% for medical therapy for the endpoints of fatal or nonfatal stroke, but the benefit was not substantiated for patients older than 75 years of age.

Based on the current guidelines, controversy still surrounds the selection of asymptomatic patients for CEA. Given the low risk for stroke for all deciles until 80% to 89% carotid artery stenosis demonstrated by the European Carotid Artery Surgery Trialists (European Carotid Surgery Trialists' Collaborative Group, 1995), some experts recommend surgery only when the degree of stenosis is greater than 80%, provided that the operation is performed by an experienced surgeon with a complication rate (combined arteriography and surgical) of 3% or less. Additionally, current guidelines state that CEA for asymptomatic carotid artery disease is proven only for patients 40 to 75 years of age with very well-defined clinical characteristics, while women with either asymptomatic or moderate (50% to 69%) symptomatic carotid artery disease seem to derive a less clear benefit from CEA as opposed to men (Chaturvedi et al., 2005).

The value of impaired cerebral vasomotor reactivity using IV administration of acetazolamide as a predictor of stroke risk in patients with asymptomatic carotid artery stenosis is controversial. The necessity for widespread screening of patients with asymptomatic carotid artery stenosis is not supported by available data. Although concomitant CEA and coronary artery bypass grafting can be achieved with acceptably low operative risk, the risk is higher for combined procedures, and the best management for symptomatic patients with carotid stenosis and coexisting severe carotid and coronary artery disease is still unknown (Pullicino and Halperin, 2005). The risk for postoperative events related to carotid

artery stenosis, compared with combined CEA (or stent) and surgery, seems to be low for asymptomatic carotid stenosis patients, and available data do not justify preoperative prophylactic CEA in patients requiring coronary angioplasty.

Stenting of the Carotid Artery and Other Cervicocerebral Vessels

Carotid artery angioplasty and stenting (CAS) has emerged as an alternative treatment to CEA, particularly in patients with internal carotid artery stenosis in an anatomically high location in the neck, carotid artery restenosis following prior CEA, radiation-induced carotid artery stenosis, and among certain high-risk patients with serious medical comorbidities (Mas et al., 2006). There is strong evidence for the clinical efficacy of CEA compared to medical therapy, but only recently has there been evidence suggesting that CAS is a reasonable alternative to CEA (Fig. 65.30).

Early CAS trials did not show benefit as compared with CEA in reducing stroke or death related to carotid artery stenosis. The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) study reported that in high-risk patients who would have been ineligible for enrollment in NASCET or ACAS, CAS was not inferior to CEA (Yadav et al., 2004). Between August 2000 and July 2002, 747 patients were enrolled in the study, and 334 patients underwent randomization. Of the 413 patients who were not randomly assigned to treatment, 406 were entered into the stent

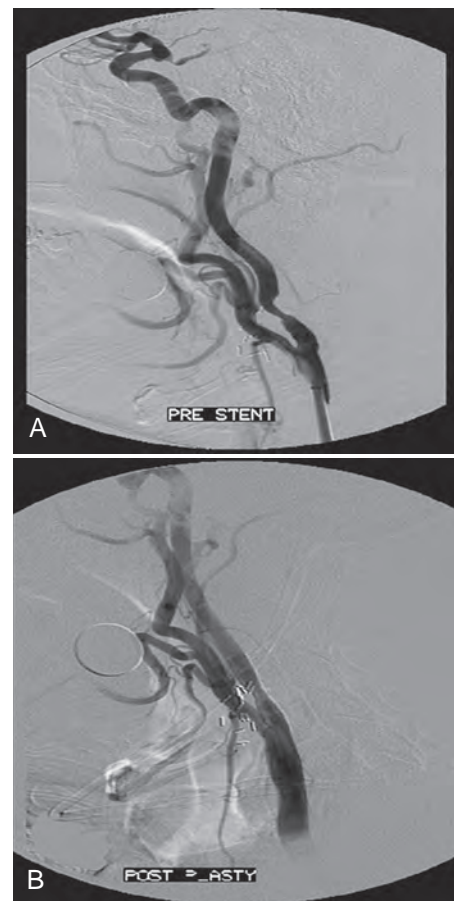



Fig. 65.30 A 76-year-old man with 55% symptomatic right carotid artery stenosis presenting with decreased sensation on the left face, arm, and leg. **A**, The pre-stent cervical carotid artery. **B**, Same artery post stent.

registry, and seven were entered into the surgical registry. The overall primary event rate of stroke, myocardial events, or death at 30 days in the randomized trial was high, with a cumulative 30-day event rate of 12.2% in the CAS arm and 20.1% in the CEA arm. The study conclusion was that CAS was not inferior to CEA, but there was no nonprocedural (medical) arm to serve as a baseline comparator.

Thereafter, two European studies, the Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy (SPACE) and the Endarterectomy versus Stenting in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) suggested that CAS was inferior to CEA. Arguments regarding the generalizability of these results, secondary to issues with study design and proceduralist capabilities, failed to resolve the debate regarding the relative merits of CEA versus CAS.

The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST), a North American-based study, showed that among patients with either symptomatic or asymptomatic carotid artery stenosis, the risk of stroke, MI, or death did not differ statistically between those patients who underwent CEA or CAS (Brott et al., 2010). The overall 4-year rate was 7.2% for CAS and 6.8% for CEA. There was no difference by sex or symptomatic status, but older patients fared better with CEA because of a lower stroke rate. Younger patients by contrast fared better with CAS as a result of a lower MI rate. Furthermore, there was a greater periprocedural stroke (CEA 2.3% vs CAS 4.3%; $P = 0.01$) or death rate in the CAS group (death; 0.3% CEA vs 0.7% CAS; $P = 0.18$) and a greater MI (2.3% CEA vs 1.1% MI; $P = 0.03$) in the CEA group.

In contrast to CREST, the ICSS, a European study of 1713 patients with symptomatic carotid artery stenosis reported a 30-day risk of stroke or death of 8.5% after CAS, versus 4.7% after CEA (hazard ratio, 1.86; 95% CI, 1.26–2.74; $P = 0.001$) (International Carotid Stent Study Investigators, 2010). In a substudy of 231 patients, there was a threefold excess risk of new ischemic lesions on DW-MRI in those patients who underwent CAS (Bonati et al., 2010). Furthermore, embolic protection devices did not protect CAS patients from developing new ischemic lesions. Thus, even though the CREST study suggests that CAS may be of benefit in selected patients when done by experienced proceduralists, the relative merit of CEA versus CAS remains a matter of considerable debate.

 An extended version of this section and eFig. 65.31 can be found at <http://www.expertconsult.com>.

GENERAL MANAGEMENT OF ACUTE ISCHEMIC STROKE

Rapid diagnosis of stroke and initiation of treatment are important to maximize recovery, prevent recurrence of stroke, and prevent complications. Patients with a TIA or an acute stroke, regardless of severity, presenting within 72 hours of symptom onset should be admitted to the hospital for emergency evaluation and treatment, preferably in a stroke unit or intensive care unit where close medical and nursing observation is available. Treatment of unselected acute stroke patients in specialized stroke units correlated with a lower mortality rate, reduced length of hospital stay, reduced frequency of discharge to a nursing home, and potentially reduced cost. Development of a stroke team is advantageous to expedite emergency care. Emergency care involves attention to the protection of the airway to avoid obstruction, hypoventilation, and aspiration. Pulse oximetry or arterial blood gases may be indicated. Supplemental oxygen and ventilatory assistance should be added if needed. Mild hypothermia protects the brain from ischemic injury; hyperthermia worsens ischemic outcome. Prevention of pulmonary complications is necessary

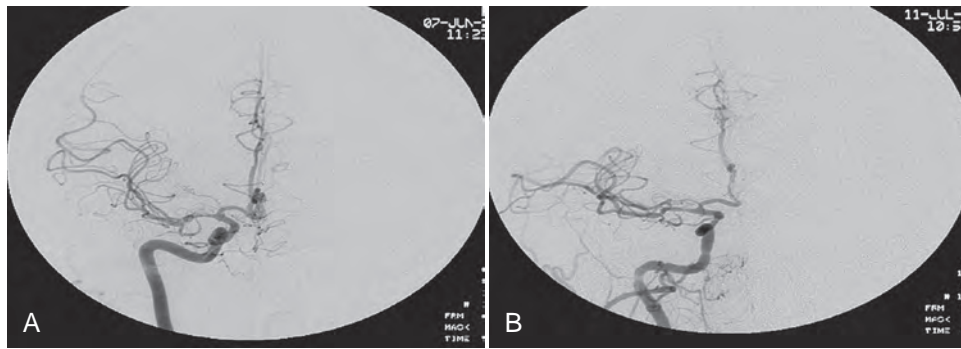
in the bedridden patient or in the patient with impaired oropharyngeal function. The mortality rate from pneumonia is as high as 15% to 25% in stroke patients. Aspiration was documented by video-fluoroscopic modified barium swallow examination in more than a third of patients with brainstem strokes, in one-fourth with bilateral hemispheric strokes, and one-tenth of patients with unilateral hemispheric strokes. If there is evidence of oropharyngeal dysfunction, it is important to place a temporary enteral feeding tube for administration of nutrition and enteral medication to minimize the risk for aspiration. Patients with oropharyngeal dysfunction, even if it appears to be mild, should receive nothing by mouth until evaluated by an experienced speech pathologist and until appropriate swallowing studies are completed. Frequent suctioning and maintenance of the head of bed greater than 30 degrees may help prevent aspiration of oral secretions.

The next step is assessment of the circulation. This involves evaluation of cardiac function and blood pressure. Because of the high frequency of cardiac dysfunction associated with stroke, cardiac monitoring is recommended for at least 48 hours after stroke. An immediate 12-lead ECG and troponin level should be obtained. Concomitant cerebral and myocardial ischemia can occur in approximately 3% to 20% of cases. Ischemic stroke can be complicated by a variety of cardiac arrhythmias. If ischemic ECG changes occur or abnormal cardiac troponin levels are noted on admission, serial ECG and cardiac troponins are indicated. In patients with stroke, the blood pressure should be monitored frequently or even continuously for the first 48 to 72 hours. It is not unusual for the blood pressure to be transiently elevated after a stroke. Optimal arterial blood pressure post stroke appears to range from 160 to 200 mm Hg for SBPs and 70 to 110 mm Hg for DBPs (Castillo et al., 2004). Lower or higher arterial blood pressures were otherwise associated with an increased volume of stroke on CT scan 4 to 7 days post stroke. Following an acute event, the arterial blood pressure may return to prestroke levels within a few days. Whether transient elevations should be treated is controversial. It is important to not over-treat the blood pressure and cause hypotension. The most important objective is to maintain adequate cerebral blood flow in the presence of impaired autoregulation. If urgent lowering of the blood pressure is indicated, IV labetalol can be given (e.g., 10 mg over 1–2 minutes, repeated or doubled every 10–20 minutes until the desired response has been achieved or a maximum dosage of 300 mg has been administered). Contraindications to the use of labetalol include congestive heart failure, asthma, second- or third-degree heart block, or cocaine use. Nicardipine may be a reasonable alternative IV agent. Therapy is usually initiated at 5 mg/h, and the infusion is titrated every 5 to 15 minutes by 2.5 mg/h to the desired rate, with a maximum dose of 15 mg/h. The use of immediate-release preparations of nifedipine, however, should be avoided because they lower the blood pressure in an unpredictable and sometimes dramatic fashion and have caused major cerebral infarcts. However, any blood pressure-lowering agent should be used with caution. The American Heart Association guidelines suggest lowering the arterial blood pressure immediately post stroke only if the patient's blood pressure is above 220/130 mm Hg (Jauch et al., 2013) unless the patient is a candidate for thrombolytic therapy, in which case a target goal of less than 185/110 mm Hg is appropriate prior to thrombolysis.

Immediately after the patient's arrival in the emergency room, blood should be sent for appropriate studies, including a complete blood cell count, PT (INR), APTT, and a general chemistry screen. A focused neurological examination should be performed to assess neurological stability and determine the extent of infarction. General signs that point toward a large

Stenting of intracranial arteries is still a procedure under development, although the frequency of ischemic stroke related to intracranial stenosis may be as high as that attributable to extracranial disease (Chimowitz et al., 1995). The procedure is not without risk, and compared to medical therapy, the rate of restenosis and other complications is not yet low enough to justify this procedure except in the context of clinical trials, although advocates have suggested that intracranial stenting is appropriate in cases with recurrent events despite aggressive medical therapy (Higashida et al., 2005). Two small single-arm studies have been published. In the Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries (SSYLVIA) study, restenosis occurred in 12 of 37 (32.4%) intracranial cases and 6 of 14 (42%) extracranial vertebral artery stent cases; 39.1% of the restenosis cases were symptomatic (SSYLVIA Investigators, 2004), with a stroke rate of 4 in 55 (7.3%) within 6 months. In the WINGSPAN

study, 45 patients underwent device placement for recurrent symptoms despite medical therapy (Higashida et al., 2005). Restenosis was low with this device, but the average stroke/death rate was 7.1% at 6 months (eFig. 65.31). The National Institute of Neurological Disorders and Stroke (NINDS) stopped enrollment early after 451 patients had been randomized in the Stenting vs Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial. Data indicated that aggressive medical management alone was superior to angioplasty combined with stenting in patients with symptomatic high-grade (equal or greater than 50%) intracranial arterial stenosis. Fourteen percent of patients in the angioplasty/stent arm experienced a stroke or died within the first 30 days of enrollment compared with 5.8% of patients treated with medical therapy alone (NINDS Clinical Alert 2011).



eFig. 65.31 A 56-year-old man who had a transient ischemic attack and two ischemic strokes in the right middle cerebral artery (MCA) distribution. Because of recurrent strokes, despite optimal medical therapy in the context of a 65% to 70% focal stenosis of the M1 segment of the right MCA, the patient underwent placement of a Wingspan intracranial stent. **A**, The pre-stent proximal MCA stenosis. **B**, The immediate post-stent angiogram (note the wire in place following stent deployment).

infarction are forced eye deviation, hemiplegia, and altered consciousness. An NIHSS value of greater than 15 is another general indicator of a large infarction. Once stability of the airway, breathing, and circulation is determined and a focused neurological examination is performed to assess neurological stability, the patient should be sent immediately for emergent brain imaging with cranial CT scan without contrast or MRI. This can point the way to treat the patient with tPA or to avoid antithrombotics in patients with intracranial bleeds.

Optimal target blood glucose levels in acute stroke patients remain largely unknown (Gray et al., 2004; Van den Berghe et al., 2006). The UK Glucose Insulin in Stroke Trial (GIST-UK) failed to demonstrate any clinical benefit of insulin-induced euglycemia (target glucose 72–126 mg/dL). Furthermore, mortality appeared to be higher among patients with the greatest glucose reduction (Gray et al., 2009). Moreover, in the Spectroscopic Evaluation of Lesion Evolution in Stroke: Trial of Insulin for Acute Lactic Acidosis (SELESTIAL), the infusion of glucose-potassium-insulin did not have a favorable impact on cerebral infarct growth (McCormick et al., 2010).

Attention should be directed not only to treating the stroke but also to preventing complications. A variety of neurological and medical complications can arise after a stroke. During the first week after an acute cerebral infarction, the most common cause of deterioration is development of brain edema. Brain edema begins to develop within the first several hours after an ischemic event and reaches its peak 72 to 120 hours after the stroke. Ischemic edema is initially cytotoxic and later vasogenic. Cytotoxic edema involves predominantly the gray matter, whereas vasogenic edema involves predominantly the white matter. Those at greatest risk for development of brain herniation due to edema are younger patients and those with large infarctions, often caused by large-artery occlusions. No specific pharmacological agent has been proven effective against ischemic cerebral edema. Corticosteroids are not indicated for acute ischemic stroke. Traditional treatment of increased intracranial pressure associated with acute ischemic stroke is shown in Box 65.8. In some circumstances of malignant cerebral edema associated with large hemispheric ischemic infarction, hemicraniectomy and durotomy may be indicated (Gupta et al., 2004; Juttler et al., 2007; Schneck et al., 2006; Vahedi et al., 2007a; Vahedi et al., 2007b) (Fig. 65.32). For cerebellar strokes with edema and herniation, posterior fossa decompression may be life saving (see Fig. 65.33). Ventriculostomy may also be performed, but it carries the risk for upward herniation of the cerebellum and brainstem.

In the second through the fourth weeks, pneumonia is the most common cause of non-neurological death. Many cases of pneumonia are caused by aspiration of food, saliva, or regurgitated gastric secretions, inert substances, or bacterial pathogens in saliva. Other potential complications include seizures, cardiac arrhythmias, MI, deep venous thrombosis, electrolyte disturbances, decubitus ulcers, and urosepsis. Cardiac dysfunction can manifest as ECG changes, arrhythmias, or myocardial ischemia.

Frequent neurological checks are essential for early recognition of neurological changes associated with herniation, recurrent or progressive stroke, or complications such as seizures. Seizures occur in a small percentage (< 5%) of patients after an ischemic stroke. Anticonvulsant medications should be initiated if a seizure occurs.

Deep venous thrombosis (DVT) in a hemiparetic limb is common. The risk for VTE persists into the post-stroke period. If there are no contraindications, low-dose subcutaneous UFH at a dosage of 5000 units twice a day or LMWH is used. The Prevention of VTE after Acute Ischemic Stroke with LMWH (PREVAIL) study showed that enoxaparin (40 mg once daily)

BOX 65.8 Medical Management Guidelines for Elevated Intracranial Pressure in Patients with Acute Ischemic Stroke

CORRECTION OF FACTORS EXACERBATING INCREASED INTRACRANIAL PRESSURE

Hypercarbia
Hypoxia
Hyperthermia
Acidosis
Hypotension
Hypovolemia

POSITIONAL

Avoidance of head and neck positions compressing jugular veins
Avoidance of flat supine position; elevation of head of bed 15 degrees

MEDICAL THERAPY

Endotracheal intubation and mechanical ventilation if Glasgow Coma Scale score \leq 8

Hyperventilation to a P_{CO_2} of 35 ± 3 mm Hg (if herniating)
Mannitol (20% solution); loading dose 1 g/kg over 30–60 min, followed by a maintenance dose of 0.5 g/kg every 4–6 h, depending on clinical status, serum osmolality, volume status, and intracranial pressure measurements, with the goal of dehydrating the brain and not the patient; maintenance of serum osmolality of 300–320 mOsm/L

Consider 23.4% hypertonic saline; loading dose 30 mL over 10–20 minutes, followed by a maintenance dose of 3% hypertonic saline, 1 mL/kg/h, titrated to a serum sodium of 150–155 meq/L*

FLUID MANAGEMENT

Maintenance of euolemia with isotonic solutions using normal saline; avoidance of glucose-containing solutions because hyperglycemia is associated with worse prognosis for stroke; replacement of urinary losses with normal saline in patients receiving mannitol

*Hypertonic saline is administered through a central line.

was superior to UFH in preventing VTE in patients with acute ischemic stroke but was associated with a small increase in extracranial hemorrhage rates (Kase et al., 2009). If heparin is contraindicated, intermittent pneumatic compression (IPC) of the lower extremities is recommended. Prophylactic doses of heparin can safely be given to patients receiving aspirin. The CLOTS 3 trial corroborated the effectiveness of IPC in reducing the risk of DVT in a wide variety of patients who were immobile following stroke (CLOTS (Clots in Legs Or sTockings after Stroke) Trials Collaboration, 2013).

The patient's nutritional status and fluid requirements should be assessed. Swallowing function should be assessed before intake of fluid or food is initiated. Patients who have significant oropharyngeal dysfunction require parenteral or tube feeding.

An extended version of this section is available at <http://www.expertconsult.com>.



CEREBRAL VENOUS THROMBOSIS

Intracranial sinovenous occlusive disease is an infrequent condition (0.5%–1% of all strokes) with a variety of causes.

Although urinary incontinence is not uncommon in the acute phase of stroke, indwelling catheters should be avoided unless absolutely necessary and should be removed at the earliest possible time to avoid urosepsis. The chronic use of an indwelling catheter should be limited to patients with urinary retention that is refractory to other treatments. In the presence of an indwelling catheter, treatment of asymptomatic bacteriuria is usually not indicated. However, for significant clinical infections with pyuria and fever, treatment is recommended. Approximately 15% of patients develop pressure sores after a stroke. Steps to avoid this complication include frequent inspection of the skin, skin cleansing, frequent turning, use of special mattresses and protective dressings, maintaining adequate nutritional status, and trying to improve the patient's mobility early on. One of the most common causes of injury to the patient with a stroke is falling. Assessments of the risk for falling should be made at regular intervals during the acute hospitalization and also during the chronic rehabilitation phase. Reduction of postprandial SBP has been associated with a higher incidence of falls and syncope. Measures should be instituted to minimize the risk for falls (Divani

et al., 2009). Shoulder subluxation can occur in hemiplegic patients. Chronic sequelae can be minimized if therapy is initiated before severe restriction of movement develops. Rehabilitation after stroke begins as soon as the diagnosis of stroke is established and any life-threatening neurological or medical complications have been stabilized (see Chapter 57). Patients are screened to evaluate whether they are candidates for rehabilitation. The criteria used to make this decision, including the stroke survivor's clinical and neurological status and social and environmental factors, are complex (Post-Stroke Rehabilitation Guideline Panel, 1995). The available evidence on the effectiveness of rehabilitation suggests that rehabilitation is beneficial to some patients, but the superiority of one type or the characteristics of patients most likely to benefit are not clear. Depressive symptoms are common after stroke, occurring in more than 25% of patients. Stroke patients should be screened for depression. Depression is more common following left hemispheric infarcts, especially in the frontal lobe, possibly caused by disruption of catecholamine pathways. Treatment with antidepressants is often successful in ameliorating symptoms.

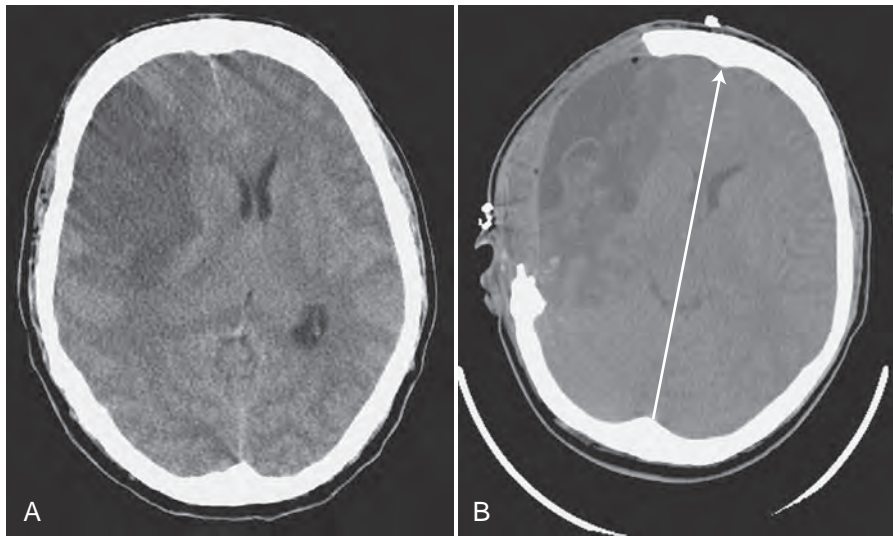


Fig. 65.32 A 50-year-old man with right internal carotid artery occlusion who had acute onset of dysarthria, right gaze preference, left facial droop, left hemiplegia, and left hemianesthesia. He had a decline in the level of consciousness from admission and was taken to surgery 48 hours post stroke for large frontal-temporal-parietal-occipital craniotomy with temporal and frontal lobectomy and durotomy. **A**, Computed tomography (CT) scan showing a right frontal infarction with subfalcine herniation. **B**, CT scan 5 days following surgery showing outward swelling of the brain, with resolution of the right-to-left midline shift.

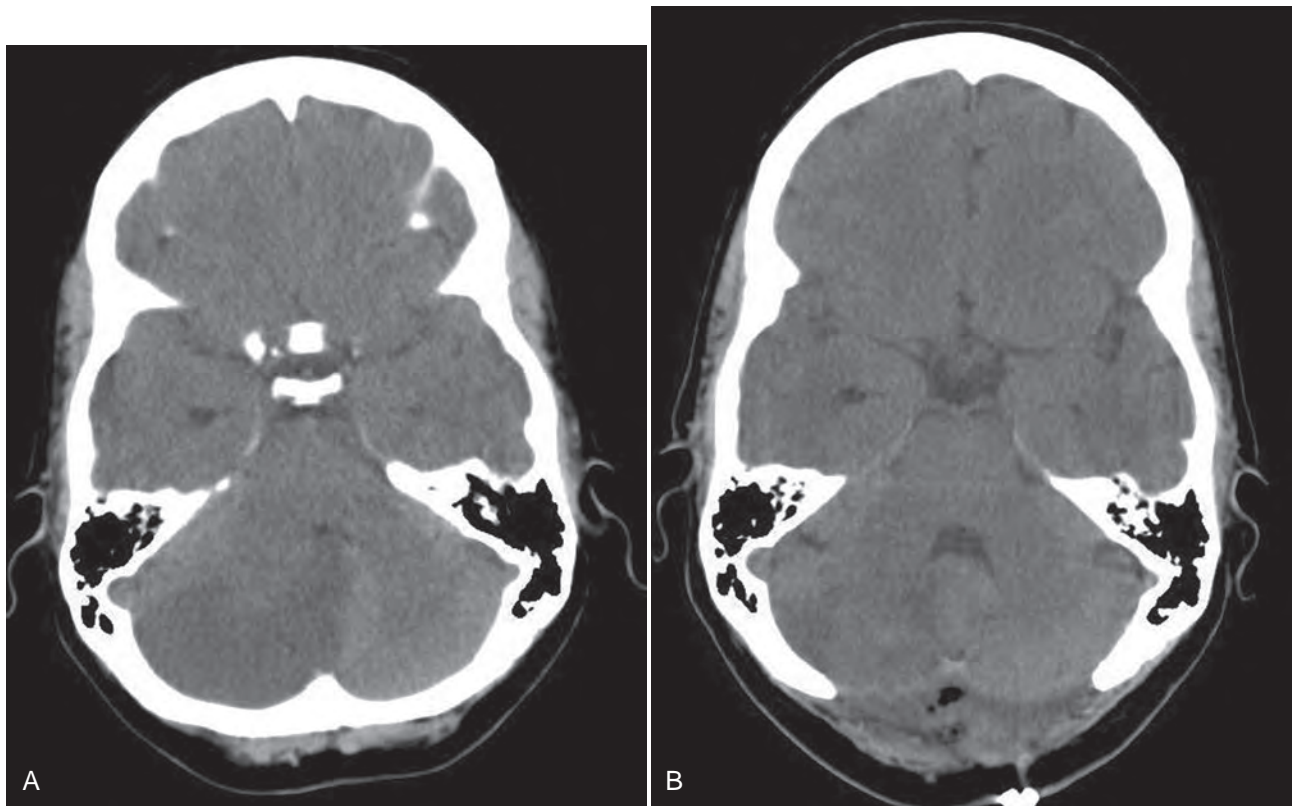


Fig. 65.33 Axial computed tomography of a 55-year-old woman showing right cerebellar infarct with mass effect causing effacement of the fourth ventricle (left panel **A**). The patient underwent suboccipital decompressive craniectomy (**B**).

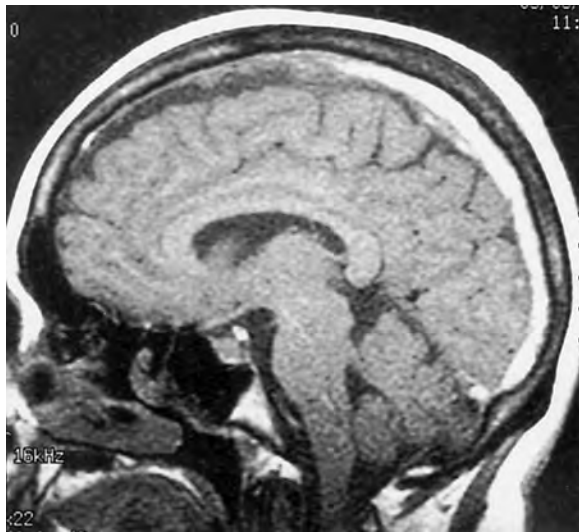


Fig. 65.35 Unenhanced sagittal T1-weighted magnetic resonance imaging shows an area of increased signal and enlargement of the superior sagittal sinus throughout most of its course, consistent with superior sagittal sinus thrombosis. It also involves the region of the torcula.

The increasing recognition of this condition is probably due to an enhanced clinical awareness and the use of MRI. Intracranial venous thrombosis can be aseptic or septic. Septic intracranial venous thrombosis (resulting from skull osteomyelitis, suppurative infections of the inner ear, and erysipelas) is relatively infrequent in modern times and most often involves the cavernous sinus. Cavernous sinus thrombosis is typically a complication of a facial or orbital infection and often presents with proptosis, chemosis, and painful ophthalmoplegia. Septic lateral sinus thrombosis is an infrequent complication of otitis media or mastoiditis and often presents with headaches, fever, otalgia, vertigo, papilledema, and abducens nerve palsy (eFig. 65.34).

Aseptic intracranial venous thrombosis is divided into dural venous sinus thrombosis, deep venous thrombosis, and superficial or cortical vein thrombosis. The superior sagittal sinus is most frequently involved (Figs. 65.35 and 65.36). Causal factors are protean and the onset often insidious. The most common causal factors are listed in Box 65.9. However, in approximately 15% to 20% of cases, no cause is found (Ferro et al., 2004). Although rare, cerebral venous thrombosis is a well-recognized disorder in children, with approximately half of cases occurring in neonates and young infants (deVeber et al., 2008).

Intracranial venous thrombosis may occur at any time from infancy to old age, but most reported modern cases have been in adult women in association with the puerperium. Onset of symptoms may be acute, subacute, or chronic. Cerebral venous infarction is the most serious consequence of cerebral venous thrombosis. Intracranial venous thrombosis should be considered a potential cause for pseudotumor cerebri or unexplained hemorrhagic infarctions. Venous infarctions are often multifocal and bilateral, affecting both the gray matter and the subcortical white matter. Evidence of cerebral edema is unusual. Cerebral venous thrombosis may present without focal signs. Chief complaints are headaches, vomiting, transient visual obscurations, focal or generalized seizures, lethargy, or coma. Papilledema is common. There may be alternating focal deficits, hemiparesis or paraparesis, or other focal neurological deficits according to the location of the venous structure

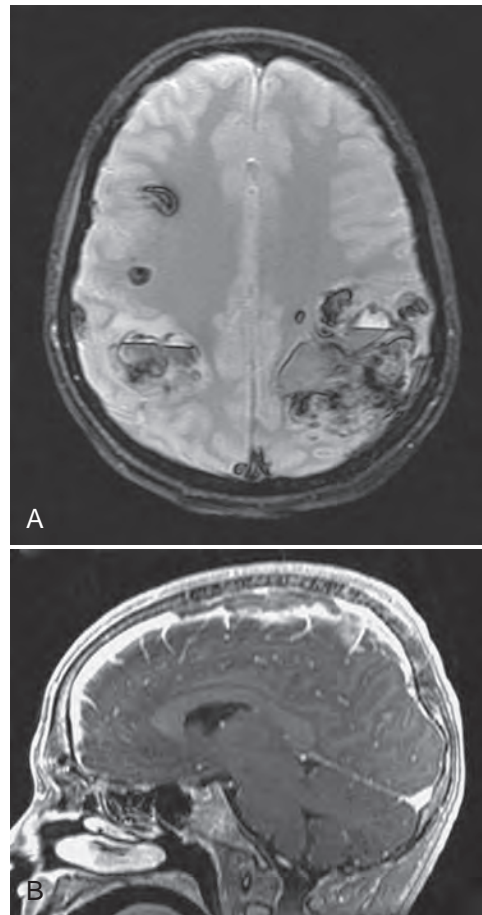
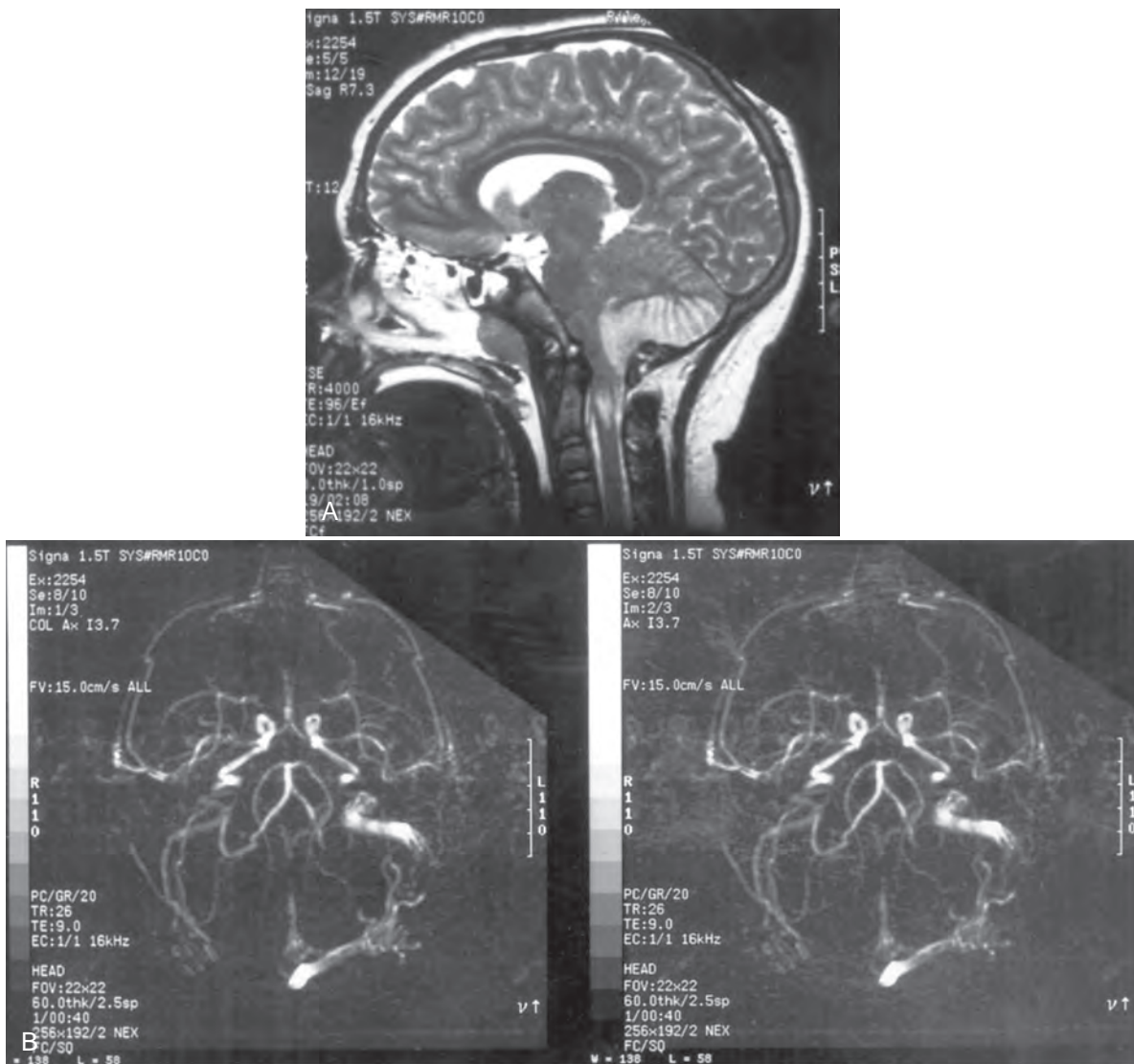


Fig. 65.36 A 14-year-old boy with newly diagnosed acute lymphoblastic leukemia was on induction therapy that included L-asparaginase. He had a generalized seizure and postictal confusion. Head computed tomography (CT) showed bilateral hemorrhagic infarctions with fluid-fluid levels. Subsequent magnetic resonance imaging (MRI) showed a superior sagittal sinus thrombosis extending into cortical veins over the superior aspect of both parietal lobes, with associated early subacute hemorrhages in both parietal lobes. **A**, Gradient echo MRI demonstrating mixed and very irregular areas of intermediate and decreased T1 signal consistent with early subacute hemorrhage in both hemispheres. **B**, Venous phase MRI demonstrating proximal filling defects in the superior sagittal sinus and extending from the coronal to the lambdoid sutures, with possible filling defects extending into cortical veins near the midline in the high parietal regions bilaterally.

involved. Salient radiological features are the presence of low-density areas of infarction, hemorrhages, and small ventricles. There may be visualization of thrombus within the sinus on postcontrast images (empty delta sign) or direct visualization of the clot. The availability of MR venography makes it possible to diagnose early and atypical cases. MR venography is a reliable diagnostic tool and has replaced angiography for the diagnosis of cerebral venous thrombosis. Patients with intracranial venous occlusive disease should be screened for thrombophilia.

Accepted therapeutic measures include reduction of increased intracranial pressure, prophylactic anticonvulsants, and antibiotics in cases involving a septic causal factor. Most recent reviews on the subject recommend IV heparin or subcutaneous LMWH followed by warfarin for the treatment of



eFig. 65.34 A 10-year-old girl with otomastoiditis was evaluated because of unresponsiveness. Magnetic resonance imaging shows areas of increased signal in the right cerebellum greater than the left cerebellum, consistent with infarctions. The cerebellar tonsils are herniated. **A**, Associated edema occurs in the superior cervical cord and inferior medulla. Phase-contrast magnetic resonance angiography (MRA) images demonstrate lack of flow in the straight sinus and the right transverse sinus. Only a small amount of signal in the region of the right sigmoid and internal jugular vein is seen. **B**, Some arterial flow is represented in the examination.

BOX 65.9 Causes of Intracranial Sinovenous Occlusive Disease

Facial/orbital/paranasal sinuses/middle ear infections	Chronic lung disease
Trichinosis	Diabetes mellitus
Syphilis	Cerebral arterial occlusions
Varicella-zoster virus infections	Homocystinuria
Human immunodeficiency virus infections	Head injury
Sepsis	Paroxysmal nocturnal hemoglobinuria
Pregnancy and puerperium	Sickle cell disease and trait
Carcinoma	Polycythemia vera
Dehydration	Essential thrombocythemia
Marasmus	Iron-deficiency anemia
L-Asparaginase therapy	Hypoplasminogenemia
Androgen therapy	Afibrinogenemia
Cisplatin and etoposide therapy	Cryofibrinogenemia
Epsilon-aminocaproic acid therapy	Antiphospholipid antibody syndrome (APAS)
Medroxyprogesterone therapy	Disseminated intravascular coagulation
Cis-diamminedichloroplatinum (CDDP) and etoposide (VP-16) therapy	Antithrombin deficiency
Intravenous catheters, cardiac pacemakers	Protein S deficiency
Polyarteritis nodosa	Protein C deficiency
Systemic lupus erythematosus	Combined deficiencies (protein C, protein S, and antithrombin III)
Granulomatosis with polyangiitis	Activated protein C resistance
Behçet disease	Factor V Leiden mutation
Kohlmeier-Degos disease (malignant atrophic papulosis)	Prothrombin G20210 mutation
Osteopetrosis	Elevated factor VIII plasma levels
Inflammatory bowel disease	Heparin-induced thrombocytopenia
Sarcoidosis	Maternal coagulopathy (twin transfusion reaction)
Osteoporosis	Familial histidine-rich glycoprotein deficiency
Congestive heart failure	Arteriovenous malformations
Nephrotic syndrome	Sturge-Weber syndrome
Budd-Chiari syndrome	Neoplasm (meningioma, metastasis, glomus tumors)
	Idiopathic

intracranial venous thrombosis (Stam et al., 2002). The efficacy of heparin has been shown even in patients who have evidence of intracranial hemorrhage by neuroimaging studies. Heparinoid therapy may be relatively contraindicated in patients with central venous thrombosis with large intracranial hematomas (Stam et al., 2003). In those instances or in patients failing to respond or who deteriorate despite anticoagulation, local infusion of thrombolytic agents and/or

thrombectomy within the occluded intracranial venous sinus may be considered (Stam, 2008). Decompressive surgery may be required in selective instances (Crassard et al., 2010; Ferro et al., 2010).

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The complete reference list is available online at <https://expertconsult.inkling.com/>.



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CHAPTER OUTLINE

MECHANISMS OF INTRACEREBRAL HEMORRHAGE

Hypertension
 Vascular Malformations
 Intracranial Tumors
 Bleeding Disorders, Anticoagulants, and Fibrinolytic Treatment
 Cerebral Amyloid Angiopathy
 Granulomatous Angiitis of the Central Nervous System and Other Vasculitides
 Sympathomimetic Agents
 Hemorrhagic Infarction
 Head Trauma

CLINICAL FEATURES OF INTRACEREBRAL HEMORRHAGE

Putaminal Hemorrhage
 Caudate Hemorrhage
 Thalamic Hemorrhage
 Lobar Hemorrhage
 Cerebellar Hemorrhage
 Pontine Hemorrhage
 Mesencephalic Hemorrhage
 Medullary Hemorrhage
 Intraventricular Hemorrhage

TREATMENT OF INTRACEREBRAL HEMORRHAGE

General Management of Intracerebral Hemorrhage
 Choice Between Medical and Surgical Therapy in Intracerebral Hemorrhage
 Hemostatic Therapy of Intracerebral Hemorrhage

Intracerebral hemorrhage (ICH) accounts for approximately 10%–20% of strokes (O'Donnell et al., 2010). Its clinical importance derives from its high frequency and 30-day mortality, which is close to 50%. The incidence of ICH has remained stable in the past 3 decades (van Asch et al., 2010), despite a gradually improved level of detection and treatment of hypertension, suggesting that ICH due to other mechanisms, such as anticoagulant use, has become more frequent (Flaherty et al., 2007). ICH continues to be a major public health problem, especially in populations at high risk such as young and middle-aged blacks and Hispanics, in whom ICH occurs more frequently than in whites, the medically indigent who lack hypertension treatment, and the elderly on anti-thrombotic therapy. A growing body of evidence suggests that genetic factors such as possessing the $\epsilon 2$ and $\epsilon 4$ alleles of the apolipoprotein E gene play an important role in the occurrence of certain forms of ICH such as lobar hemorrhages (Greenberg et al., 2004). Novel potential genetic factors predisposing to ICH continue to be added by experimental, clinical, and genome-wide association studies (Gould et al., 2006). Finally, the management of ICH is controversial as the assessment of various interventions awaits the completion of prospective clinical trials.

MECHANISMS OF INTRACEREBRAL HEMORRHAGE**Hypertension**

The main cause of ICH is hypertension. The primary role of hypertension in ICH is supported by a high frequency (72%–81%) of history of hypertension, significantly higher blood pressure measurements at admission in comparison with patients with other stroke subtypes, high frequency of left ventricular hypertrophy, and over-representation of common genetic variants associated with hypertension (Falcone et al., 2012).

In one study of 188 patients with primary ICH (i.e., excluding patients with hemorrhage associated with ruptured arteriovenous malformations [AVMs], tumor, anticoagulant and thrombolytic therapy, and cocaine ingestion), it was determined that the cause was hypertension in 72% of patients. Similarly, a multicenter international study determined hypertension as the strongest risk factor for ICH, accounting for 74% of the population-attributable risk (O'Donnell et al., 2010). Other modifiable risk factors for ICH included excessive smoking, alcohol intake, central obesity, low cholesterol levels, unhealthy diet, and sedentary lifestyle. Further support for the importance of hypertension in the pathogenesis of ICH is the steady increase in ICH incidence with advancing age, which is also associated with an increase in the prevalence of hypertension. Furthermore, mean systolic pressure increases steeply in the days leading to an ICH (Fischer et al., 2014).

The vascular lesion produced by chronic hypertension that leads to arterial rupture and ICH is probably lipohyalinosis of small intraparenchymal arteries. The role of microaneurysms of Charcot and Bouchard is uncertain, although their anatomical location at sites preferentially affected by ICH supports their causal importance. The nonhypertensive causes of ICH are listed in Box 66.1.

Vascular Malformations

Because a detailed discussion of intracranial aneurysms and AVMs is provided elsewhere (see Chapter 67), the analysis is limited here to the role of small vascular malformations in the pathogenesis of ICH. These lesions are often documented by magnetic resonance imaging (MRI), by pathological examination of specimens obtained at the time of surgical drainage of ICHs, or at autopsy. However, cerebral angiography also plays an important role in the diagnosis of these lesions.

ICHs caused by small AVMs or cavernous angiomas are frequently located in the subcortical white matter of the cerebral hemispheres. The clinical presentation of the ICH in this setting has a few distinctive characteristics: the hematoma is generally smaller, and symptoms develop more slowly than with hypertensive ICH; the presence of associated subarachnoid hemorrhage on CT scan suggests an aneurysm or AVM as the cause of a lobar ICH; and ICHs associated with small vascular malformations generally tend to occur in younger patients than those with hypertensive ICH, and have a female preponderance.

Cavernous angiomas are often recognized by MRI as a cause of ICH in the subcortical portions of the cerebral

BOX 66.1 Nonhypertensive Causes of Intracerebral Hemorrhage

Vascular malformations (saccular or mycotic aneurysms, arteriovenous malformations, cavernous angiomas)
 Intracranial tumors
 Bleeding disorders, anticoagulant and fibrinolytic treatment
 Cerebral amyloid angiopathy
 Granulomatous angiitis of the central nervous system and other vasculitides, such as polyarteritis nodosa
 Sympathomimetic agents (including amphetamine and cocaine)
 Hemorrhagic infarction
 Head trauma
 Miscellaneous: other vasculopathies (e.g., moyamoya disease, reversible cerebral vasoconstriction syndrome, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy [rarely]), and septic emboli/arteritis in the setting of infective endocarditis (all discussed elsewhere)

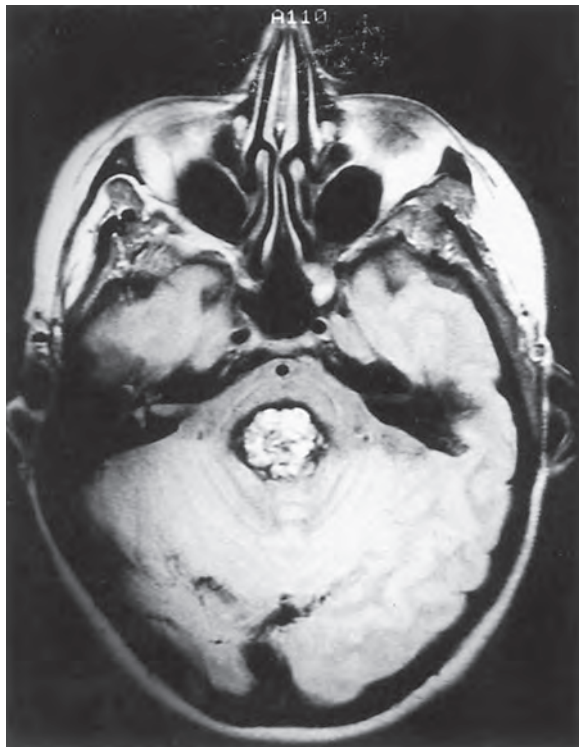


Fig. 66.1 Magnetic resonance imaging (proton density) of large cavernous angioma of the midpons in axial view, showing mixed-signal central nidus with peripheral hemosiderin ring.

hemispheres and in the pons. This technique demonstrates a characteristic pattern on T2-weighted images, with a central nidus of irregular bright signal intensity mixed with mottled hypointensity (the “popcorn” pattern), surrounded by a peripheral hypointense ring corresponding to hemosiderin deposits (Fig. 66.1), reflecting previous episodes of blood leakage at the edges of the malformation. These lesions are predominantly supratentorial, favoring the temporal, frontal, and parietal lobes, whereas the less frequent infratentorial locations favor the pons. They are generally single lesions, but multiplicity is not rare, especially in patients with familial cavernous angiomas. Familial clustering is common among

individuals of Mexican descent, in whom cavernous angiomas are inherited in an autosomal dominant pattern linked to a mutation in gene CCM1 in chromosome 7q (Gault et al., 2006). Cavernous angiomas manifest with seizures (27%–70%), ICH (10%–30%), or focal neurological deficits (29%–35%). ICH occurs in both the supratentorial and infratentorial varieties. A progressive course due to recurrent small hemorrhages within and around the malformation is occasionally seen in posterior fossa (especially pontine) lesions, and the deficits can evolve over protracted periods, at times suggesting a diagnosis of multiple sclerosis or a slowly growing brainstem tumor.

A clinical profile thus can be suggested for cases of ICH due to small vascular malformations. These occur in generally young, predominantly female patients who present with a syndrome of lobar ICH in which CT may document a superficial lobar hematoma with adjacent local subarachnoid hemorrhage, or MRI demonstrates the characteristic features of a small AVM or cavernous angioma. Lack of documentation of the vascular malformation on angiography is the rule—especially in the slow-flow cavernous angiomas—and definite diagnosis requires either MRI or the histological examination of a sample of the hematoma and its wall.

The overall annual rate of ICH in persons with cavernous angiomas is 0.15–6%, with higher rates reported in persons initially manifesting with hemorrhage and lower rates in incidental cases found on neuroimaging (Al-Shahi Salman et al., 2012; Flemming et al., 2012). The risk of recurrent hemorrhage is highest in the first 2 years following initial ICH and occurs more frequently in women.

Intracranial Tumors

Bleeding into an underlying brain tumor is relatively rare in series of patients presenting with ICH, accounting for less than 10% of the cases. The tumor types most likely to lead to this rare complication are glioblastoma multiforme or metastases from melanoma, bronchogenic carcinoma, choriocarcinoma, or renal cell carcinoma (Fig. 66.2). The ICHs produced in this setting may have clinical and imaging characteristics that should suggest an underlying brain tumor, including: (1) the presence of papilledema on presentation, (2) the location of ICH in sites that are rarely affected in hypertensive ICH, such as the corpus callosum, which in turn is commonly involved in malignant gliomas (Fig. 66.3), (3) the presence of ICH in multiple sites simultaneously, (4) a CT scan characterized by a ring of high-density hemorrhage surrounding a low-density center in a noncontrast study, (5) enhancing nodules adjacent to the hemorrhage on contrast CT or MRI, and (6) a disproportionate amount of surrounding edema and mass effect associated with the acute hematoma. In these circumstances, a search for a primary or metastatic brain tumor should follow and include evaluation for systemic malignancy; if there is none, cerebral angiography and eventually craniotomy for biopsy of the wall of the hematoma cavity should be considered. Confirmation of the diagnosis of ICH secondary to malignant brain tumor carries a dismal prognosis, with a 30-day mortality rate in the 90% range.

Bleeding Disorders, Anticoagulants, and Fibrinolytic Treatment

Bleeding disorders due to abnormalities of coagulation are rare causes of ICH. Hemophilia caused by factor VIII deficiency leads to ICH in approximately 2.5% to 6.0% of patients, half with ICH and half with subdural hematomas. The majority of these hemorrhages occur in young patients, generally younger than age 18, and their mortality is high,