

# HOSPITAL PHYSICIAN®

## NEUROLOGY BOARD REVIEW MANUAL

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## Ischemic Stroke: Pathophysiology and Principles of Localization

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# Ischemic Stroke: Pathophysiology and Principles of Localization

Matthew Brandon Maas, MD, and Joseph E. Safdieh, MD

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## INTRODUCTION

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Stroke is a sudden loss of neurologic function resulting from focal disturbance of cerebral blood flow due to ischemia or hemorrhage. Depending on the duration of the cerebrovascular disturbance, stroke can cause permanent neurologic damage, disability, or death. A transient ischemic attack (TIA; stroke symptoms lasting < 1 hr) may not cause neurologic damage but is strongly associated with a risk for subsequent stroke within the next 90 days. Stroke is the third leading cause of death in the United States, with only heart disease and cancer accounting for more mortality.<sup>1</sup> Ischemic stroke accounts for 87% of all strokes.<sup>1</sup> Among persons aged 45 to 64 years, 8% to 12% of ischemic strokes result in death within 30 days.<sup>1</sup>

Although a life-threatening emergency, ischemic stroke is a treatable condition; the degree of disability is linked with response to treatment. The adept clinician must efficiently synthesize a broad array of clinical data to make rapid decisions when managing this critically ill population. Despite an ever-growing arsenal of sophisticated neuroimaging techniques and laboratory studies for managing suspected stroke, the clinical approach to these patients remains firmly grounded in its dependence on the core principles of neurology: diagnosis of the disease process and lesion localization based on history and neurologic examination.

This manual, the first part of a 2-part review of ischemic stroke, provides an overview of stroke pathophysiology and principles of stroke localization. The next manual will discuss the approach to evaluation of a patient with suspected ischemic stroke, acute and later-stage treatment of ischemic stroke, and strategies for prevention.

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## PATHOPHYSIOLOGY OF ISCHEMIC STROKE

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### MECHANISMS OF ISCHEMIA

Although there are many etiologic mechanisms, the common pathway of ischemic stroke is lack of sufficient

blood flow to perfuse cerebral tissue. Interruption of forward blood flow at any point can lead to irreversible neuronal damage. The mechanisms of ischemia can generally be divided into 5 main categories: thrombosis, embolism, systemic hypoperfusion, arterial luminal obliteration, and venous congestion. Cerebral venous thrombosis can lead to vascular congestion, impairment of forward flow, and eventually infarction. The evaluation and management of venous thrombosis requires many unique considerations in contrast to arterial etiologies and is beyond the scope of this review. Ischemic stroke mechanisms in the other 4 main categories are summarized in **Table 1** and discussed in more detail below.

Many classification schemes exist for assigning an etiologic mechanism for ischemic stroke, the most widely used of which is TOAST (a set of criteria originally developed for the Trial of Org 10172 in Acute Stroke Treatment).<sup>2</sup> The refined and updated TOAST criteria, known as SSS-TOAST, use a combination of historical, laboratory, cardiovascular, and neuroimaging data to assign a mechanism using a degree of certainty derived from the annual or one-time primary stroke risk threshold for each evaluated factor based on best evidence from the literature. Causative mechanisms are grouped into 1 of 5 categories: large artery atherosclerosis, cardioaortic embolism, small artery occlusion, other causes (an identified cause recognized as an etiology for stroke, such as arterial dissection), or undetermined based on descriptive criteria.<sup>3</sup>

### Thrombosis

In situ thrombosis is the formation of a clot in an artery that persists long enough to cause ischemic insult to the cerebral tissue supplied by the affected vessel. Thrombosis is often triggered by pathology in the local endothelium. Atherosclerotic plaques are inherently prothrombotic, overexpressing plasminogen activator inhibitor-1 (the main inhibitor of tissue plasminogen activator) and tissue factor. *Chlamydia pneumoniae* is associated with atherosclerotic plaques, and further inflammatory activity is attributable to activated macrophages and T cells that congregate in high-shear regions. In

**Table 1.** Arterial Etiologies of Ischemic Stroke

Systemic Hypoperfusion	Thrombosis	Embolism	Luminal Obliteration
Massive MI	Atherosclerotic plaque rupture	<b>Artery-to-artery</b>	<b>Noninflammatory vasculopathy</b>
Symptomatic cardiac arrhythmia	Small-vessel lipohyalinosis	Atheroma fragments (thrombus from dissection site)	Moyamoya disease
Shock			CADASIL
Severe hypotension with proximal stenosis	Vascular invasion by tumor	<b>Cardioaortic</b>	Sneddon syndrome
Hyperviscosity syndrome	HIT type II	Cardiac thrombus fragments	Fibromuscular dysplasia
	Sickle cell disease	Endocarditis vegetations (mycotic)	Thromboangiitis obliterans (Burger's disease)
	TTP	Cholesterol	Malignant atrophic papulosis (Köhlmeier-Degos disease)
	DIC	Tumor	Sickle cell disease
	Antiphospholipid antibody syndrome	<b>Decompression illness</b>	Migraine
		<b>Paradoxical</b>	<b>Extrinsic artery compression</b>
		Air	Herniation
		Cholesterol (especially post-fracture)	Masses
		Deep venous thrombus fragments	<b>Vasculitis</b> (see Table 3)
		Amniotic fluid	<b>Vasospasm</b>
			Subarachnoid hemorrhage
			Meningitis
			Drug-induced (Call-Fleming syndrome)
			<b>Angiotrophic lymphoma</b>
			Intravascular lymphoma
			Lymphomatoid granulomatosis

CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; DIC = disseminated intravascular coagulation; HIT = heparin-induced thrombocytopenia; MI = myocardial infarction; TTP = thrombotic thrombocytopenic purpura.

large-vessel thrombosis, the luminal aspect of atheromatous plaques can be degraded by metalloproteinases, leading to rupture and creating an ulcerated lesion with highly thrombogenic properties. Ulceration can lead to in situ thrombosis or embolization of thrombotic material at the site of ulceration.<sup>4</sup> In smaller vessels (400–900 μm in diameter), microatheromatosis results in lacunar infarcts. Vessels less than 200 μm in diameter develop lipohyaline deposition in the media as well as fibrous intimal proliferation from prolonged exposure to hypertension or hyperglycemia, leading to small lacunar infarcts that are often asymptomatic.<sup>5</sup>

In heparin-induced thrombocytopenia type II, immune-mediated platelet dysfunction may lead to stroke by thrombosis of already prothrombotic atherosclerotic cerebral arteries, or by embolism of platelet aggregates (white clots) into vessels without angiographic evidence of atherosclerosis.<sup>6</sup> Thrombotic thrombocytopenic purpura leads to diffuse ischemia due to thrombosis of vessels in the microcirculation. The clinical result is a waxing and waning syndrome of mostly non-focal deficits, headache, seizures, and encephalopathy. In antiphospholipid antibody syndrome, patients are at increased risk for both venous and arterial thrombosis. Strokes tend to be cortical and subcortical and associat-

ed pathologically with arteriolar thrombosis, although embolism from cardiac thrombi likely occurs as well.<sup>7</sup>

### Embolism

**Table 2** lists recognized sources of cerebral emboli.<sup>3,8</sup> Although the heart is the most common source of a thromboembolus, several types of material can be carried to the brain through the cerebral circulation and lodge in a vessel, leading to stroke. Stasis in the posterior left atrium and appendage, associated with atrial fibrillation or flutter, creates a high-risk environment for thrombus formation.<sup>9</sup> In the case of infectious endocarditis, vegetations composed of a mixture of platelets, fibrin, and bacteria can fragment, sending emboli into the cerebral circulation. Nonbacterial thrombotic (marantic) endocarditis can occur in the context of malignancy or other inflammatory conditions. Atheromatous plaques in the aorta and carotid arteries can ulcerate or be mechanically disrupted (during intravascular procedures or cross-clamping for cardiopulmonary bypass), leading to embolization of cholesterol and thrombi. This is known as *artery-to-artery embolization*. Artery-to-artery embolization also occurs in the context of arterial dissection due to the thrombus that forms at the site of endothelial disruption.

**Table 2.** Sources of Cerebral Emboli

High risk sources	Low risk sources
Left atrial thrombus	Mitral annular calcification
Left ventricular thrombus	Patent foramen ovale
Atrial fibrillation	Atrial septal aneurysm
Paroxysmal atrial fibrillation	Atrial septal aneurysm and patent foramen ovale
Sick sinus syndrome	Left ventricular aneurysm without thrombus
Sustained atrial flutter	Spontaneous left atrial echo contrast (smoke)
MI $\leq$ 1 month prior	Pulmonary arteriovenous malformation
Rheumatic mitral or aortic valve disease	
Bioprosthetic or mechanical heart valves	Variable risk sources
Chronic MI with ejection fraction $<$ 28%	Hypercoagulable state
Symptomatic congestive heart failure with ejection fraction $<$ 30%	Inherited thrombophilia
Dilated cardiomyopathy	Antiphospholipid antibodies
Nonbacterial thrombotic endocarditis	Cancer
Infective endocarditis	
Papillary fibroelastoma	
Left atrial myxoma	
Arterial dissection	

MI = myocardial infarction. (Data from Ay H, Furie KL, Singhal A, et al. An evidence-based causative classification system for acute ischemic stroke. *Ann Neurol* 2005;58:688–97; and Doufekias E, Segal AZ, Kizer JR. Cardiogenic and aortogenic brain embolism. *J Am Coll Cardiol* 2008;51:1049–59.)

The lungs are the brain’s most important ally in protecting against embolization from the systemic circulation. The pulmonary microcirculation functions as a fine filter for all material released into the circulation by the body. Whether dislodged fragments of a deep venous thrombus or small amounts of air introduced by an intravenous line, the material is effectively trapped in the pulmonary capillary bed and cleared. Conditions such as pulmonary arteriovenous fistula and, more commonly, patent foramen ovale allow bloodborne material to bypass the pulmonary capillary bed. The result is paradoxical embolization—brain embolism by material that originates in regions of the body other than the left heart, aorta, or vertebrobasilar or carotid arteries. Embolism by other mechanisms is rare but not unknown. Such mechanisms include direct embolization of lung tumor tissue and diffuse air (actually nitrogen) embolization in decompression sickness (caisson disease, “the bends”).<sup>10,11</sup>

### Systemic Hypoperfusion

A third mechanism of ischemic stroke is systemic hypoperfusion due to a generalized loss of arterial pres-

sure. Several processes can lead to systemic hypoperfusion, the most widely recognized and studied being cardiac arrest due to myocardial infarction and/or arrhythmia. The areas of brain at the most distal edges of the arterial tree, in the so-called *watershed region* between the main cerebral artery territories, tend to be predominantly affected. Severe hypotension can mimic the same ischemic pattern, especially in the context of significant stenosis of the common or internal carotid artery, and can lead to unilateral watershed ischemia.

### Obliteration of the Arterial Lumen

Another mechanism of ischemia is obliteration of the arterial lumen. Luminal narrowing can be driven by noninflammatory vasculopathy, inflammatory or infectious vasculitis, vasospasm, or compression by an extrinsic mass.

### Noninflammatory Vasculopathy

Several progressive noninflammatory vasculopathies are known; these are rare conditions that are mostly idiopathic or genetically based. Sickle cell disease causes ischemia of small vessels by erythrocyte sickling in the microcirculation, but most clinical strokes are due to large vessel occlusions. Endothelial damage in large vessels is believed to promote a stenotic and obliterative process. This stenosis is best appreciated by transcranial Doppler ultrasonography; stroke risk increases in tandem with increasing flow velocities. When a vessel is stenosed, thrombosis can occur by a similar mechanism as is known to occur in the microcirculation.<sup>12</sup>

Moyamoya disease is an idiopathic vasculopathy characterized by intimal fibrous thickening with widening of the internal elastic lamina. The distal internal carotid arteries and proximal anterior and middle cerebral arteries are most commonly affected. The condition is most often seen in children but can present in adulthood. Children present with ischemic strokes, but adults often present with intracerebral hemorrhages caused by the rupture of friable collateral vessels that form as the disease progresses.<sup>13</sup>

Cerebral arteriopathy leading to TIA and stroke is an uncommon complication of thromboangiitis obliterans (Burger’s disease), an idiopathic vasculopathy causing segmental inflammation in small to medium-sized arteries. The condition is strongly associated with smoking and most heavily affects the distal extremities, where progressive vasoocclusion leads to gangrene. Cerebral angiography has confirmed the same corkscrew-shaped irregular collateral vessels in the cerebral circulation as are seen in the typical peripheral vascular

cases.<sup>14</sup> Stroke due to central nervous system (CNS) vasculopathy has also been reported in malignant atrophic papulosis (Köhlmeier-Degos disease), another rare progressive vasculopathy that typically involves the skin and intestines.<sup>15</sup>

Fibromuscular dysplasia (FMD) is a nonatherosclerotic, noninflammatory hyperplasia of the arterial wall in medium to large arteries. Although FMD is a systemic condition, the renal arteries and cerebrovascular system are most commonly affected. Based on the histologic location of the hyperplasia and angiographic characteristics, 3 types of FMD have been recognized. Type 1 FMD (hyperplasia of the media) is the most common form, accounting for approximately 80% of cases. It appears as a string of beads from luminal stenosis alternating with aneurysmal outpouchings. Type 2 FMD (hyperplasia of the intima) appears as smooth arterial narrowing. Type 3 FMD (subadventitial hyperplasia), the rarest form, appears as diverticulations along one side of an arterial wall. TIA and stroke are common consequences of FMD, and both cerebral aneurysms and arterial dissection are strongly associated.<sup>16</sup>

Sneddon syndrome is a noninflammatory vasculopathy manifesting as focal cerebral infarcts and livedo reticularis/racemosa. In addition to stroke, patients experience headache, seizures, and progressive encephalopathy.<sup>17</sup> White matter lesions suggestive of ischemic change are frequently found in patients with migraine with aura. Epidemiologic evidence suggests that migraineurs with aura are at increased risk for ischemic stroke.<sup>18</sup> A minority of these patients are believed to suffer a migraine-induced stroke, defined by the International Headache Society criteria as a stroke that occurs in a patient with migraine with aura, with deficits beginning during a typical aura when the stroke deficits partly include symptoms of the aura. Strokes meeting International Headache Society criteria for migraine-induced stroke are rare.<sup>18</sup> Migraine-induced stroke is most common in the posterior cerebral artery territory, which may be a consequence of the definition requiring symptom congruence between the infarct and aura or may be due to the ischemic pathogenesis.<sup>19</sup> The exact mechanism of migraine-induced stroke is unknown.

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a genetic defect of vascular smooth muscle caused by a Notch3 gene mutation.<sup>20</sup> Symptoms begin at a mean age of 37 years, usually with TIA or stroke. Affected individuals experience subcortical strokes causing a progressive dementia and leukoencephalopathy. The prevalence of migraine and depression is also high.<sup>21,22</sup>

**Table 3.** Vasculitides of the Cerebral Blood Vessels

Inflammatory	Infectious
<b>Primary</b>	<b>Viruses</b>
Primary angiitis of the CNS	HIV
	CMV
<b>Secondary</b>	VZV
Large arteries	HSV
Giant cell arteritis	
Takayasu's arteritis	<b>Bacteria</b>
Medium arteries	<i>Mycobacterium tuberculosis</i>
Polyarteritis nodosa	<i>Haemophilus influenzae</i>
Kawasaki disease	<i>Streptococcus pneumoniae</i>
Small to medium arteries	<i>Neisseria meningitidis</i>
Wegener's granulomatosis	<i>Rickettsia</i> species
Churg-Strauss syndrome	<i>Treponema pallidum</i>
Microscopic polyangiitis	<i>Borrelia burgdorferi</i>
Small arteries	<b>Fungi</b>
Henoch-Schönlein purpura	<i>Aspergillus</i> species
Cutaneous leukocytoclastic vasculitis	<i>Coccidioides</i> species
Essential cryoglobulinemia	Mucorales species
Microcirculation	<i>Histoplasmosis capsulatum</i>
Susac's syndrome	<b>Protozoa</b>
Behçet's disease	<i>Plasmodium</i> species
Sjögren's syndrome	<i>Toxoplasma gondii</i>
Systemic lupus erythematosus	

CMV = cytomegalovirus; CNS = central nervous system; HSV = herpes simplex virus; VZV = varicella zoster virus.

### Vasculitis

Vasculitis (ie, inflammatory vasculopathy) may be infectious or autoimmune. **Table 3** lists various disorders that cause vasculitis of cerebral blood vessels.<sup>23–25</sup> Up to 5% of strokes occurring in individuals younger than age 50 years may be due to vasculitis.<sup>24</sup> In vasculitis, flow obstruction leading to cerebral ischemia is caused by inflammatory infiltrates that swell the subintimal artery wall. In primary CNS vasculitis, pathology is limited to arteries of the CNS. Focal, segmental inflammation in small to medium-sized arteries leads to both hemorrhage and infarcts. In secondary CNS vasculitis, inflammatory vasculopathy may be caused by various angiotrophic infections or systemic inflammatory diseases. Several viruses, such as varicella zoster, cause cerebral vasculitis in both immunocompetent and immunocompromised individuals. Likewise, cerebrovascular bacterial infections are well known causes of cerebral vasculitis. Meningovascular syphilis is a classic example. Common systemic inflammatory vasculopathies that

may have CNS involvement include giant cell arteritis and Wegener's granulomatosis, among several others.

Neurologic conditions that predominantly cause ischemia in the cerebral microcirculation cause headache, encephalopathy, and an accumulation of white matter leukoariosis but may also cause clinically evident stroke. In systemic lupus erythematosus, Sjögren's syndrome, and Behçet's disease, CNS involvement rarely leads to discrete stroke-like episodes. Susac's syndrome consists of encephalopathy, branch retinal artery occlusions, and hearing loss due to a microangiopathy associated with antiendothelial cell antibodies. Brain ischemia shows a predilection for the central portion of the corpus callosum.<sup>26</sup> These patients present for stroke evaluation due to acute monocular visual loss and may be misdiagnosed as having a demyelinating disorder or other form of vasculitis.<sup>27</sup>

### **Vasospasm**

Arterial vasospasm is characterized by a combination of swelling of the artery wall and contraction of smooth muscle in the media. The spasm may be pharmacologically induced or secondary to irritants in the subarachnoid space. Pharmacologically induced vasospasm and resulting stroke, also referred to as Call-Fleming syndrome, may be provoked by potent sympathomimetic drugs (amphetamines, methamphetamine, cocaine) or serotonergic drugs.<sup>28-32</sup>

Aneurysmal subarachnoid hemorrhage (SAH) is the most widely recognized precipitant of cerebral vasospasm. The incidence of vasospasm in the context of SAH is as high as 70%.<sup>33</sup> Patients with greater hemorrhage density in the area of the circle of Willis are at highest risk. Vasospasm is a delayed phenomenon in the context of SAH, with peak activity occurring 4 to 10 days post-hemorrhage.<sup>33</sup> The anterior cerebral artery territory is uniquely prone to infarction.

Other less recognized but important causes of vasospasm include bacterial meningitis and intrathecal chemotherapy. Bacterial meningitis leads to leukocyte migration into the cerebrospinal fluid in the subarachnoid space. The inflammatory milieu leads to loss of cerebrovascular autoregulation, diminished arteriolar response to carbon dioxide, and loss of blood-brain barrier integrity.<sup>34,35</sup> A distinct pattern of arterial dysfunction ensues. Vasospasm occurs first, followed by a paralytic vasodilation associated with myonecrosis, and finally stenosis due to subendothelial edema transitioning to intimal thickening.<sup>36</sup> The prevalence of vasospasm pathology is likely underappreciated in meningitis, where significant alterations in cerebral blood flow may occur in more than 80% of cases, and is asso-

ciated with cerebral infarcts, seizures, and poor clinical outcomes.<sup>37</sup> Vasospasm in conjunction with cerebral edema similar to posterior reversible encephalopathy syndrome is also reported with intrathecal chemotherapeutic agents.<sup>38</sup>

### **Extrinsic Artery Compression**

Any space-occupying lesion can compress an artery, leading to stroke. For example, occipital lobe stroke is commonly seen accompanying uncal herniation due to compression of the entrapped posterior cerebral artery. Intravascular lymphoma, a rare form of B-cell lymphoma, can present as TIAs or strokes before evolving to a progressive dementia.<sup>39,40</sup> Lymphomatoid granulomatosis, an angiotrophic T-cell lymphoma, can lead to a similar clinical picture.<sup>41</sup>

### **Metabolic Causes**

Finally, metabolic failure of neurons may result from intrinsic metabolic defects rather than cerebrovascular lesions. This scenario occurs in many diseases due to inborn errors of metabolism, but most of these conditions show diffuse and progressive neurologic dysfunction rather than discrete stroke-like episodes. Mitochondrial encephalomyopathy lactic acidosis and stroke-like episodes (MELAS) is a mitochondrial disorder characterized by headache, seizures, muscle fatigability, and stroke-like episodes that usually involve the occipital lobes. The pathogenesis of the stroke-like episodes is not fully elucidated, although the syndrome causes a mitochondrial arteriopathy of small cortical arteries. Use of magnetic resonance imaging may be helpful, as MELAS-associated cerebral lesions have been reported to increase diffusion-weighted imaging signal without reducing the apparent diffusion coefficient.<sup>42</sup> MELAS typically becomes clinically evident in children.

### **CELLULAR PATHOPHYSIOLOGY**

A review of ischemic stroke pathophysiology would be incomplete without a brief description of the cellular response to ischemia. The brain accounts for 2% of body weight but 20% of total oxygen consumption. Approximately 70% of the metabolic demand in the brain is due to the Na<sup>+</sup>/K<sup>+</sup>-ATPase pump that maintains the ion gradient responsible for neuronal membrane potential. Under ischemic conditions, mitochondrial production of ATP ceases and intracellular ATP stores deplete within 2 minutes. Cell membranes depolarize, leading to a large influx of calcium and sodium and an efflux of potassium. Cells in the infarct core are rapidly and irreversibly destroyed by lipolysis, proteolysis, and disaggregation of microtubules due to metabolic failure. The ischemic

penumbra—the zone of tissue between the infarct core and normal brain—experiences diminished blood flow but preserved cellular metabolism. The goal of acute stroke therapies is to normalize perfusion and intervene in the cascade of biochemical dysfunction to preserve the maximal amount of penumbral tissue.<sup>43,44</sup>

Another consequence of membrane depolarization is the release of neurotransmitters. Massive glutamate release, along with failure of glutamate reuptake mechanisms in neurons and glia, leads to calcium influx in nearby neurons via stimulation of *N*-methyl-D-aspartate receptors. This influx of excessive calcium, termed *excitotoxicity*, can lead to death of cells that may otherwise have survived ischemia. Cortical spreading depressions emanate from the infarct core, causing sustained depolarization in nearby tissue, further feeding the release of glutamate and excitotoxicity. As cellular metabolism becomes more deranged and mitochondrial activity ceases, a cascade of increasing oxidative and nitrate stress and inflammation begins, causing tissue on the periphery of the infarct core to succumb via apoptosis.

The ion pump and channel failures resulting from ATP depletion lead to greater sodium and chloride influx than potassium efflux. There is a net passive movement of water into the cell following those ions, leading to cytotoxic edema. This cytotoxic edema can be demonstrated as one of the earliest neuroimaging findings in ischemic stroke, namely restriction of water diffusion as increased signal on the magnetic resonance diffusion-weighted image sequence. Edema is later visible as hypodensity on computed tomography imaging.

In summary, the key concepts in cellular pathophysiology relate to the brain's dependence on aerobic metabolism. The brain uses a disproportionate amount of oxygen by weight, expending the majority of energy on maintaining ion gradients across the neuronal membrane. Profound ischemia results in necrosis, and less severe ischemia triggers a series of perturbations that may lead to apoptosis in the stroke penumbra, including cortical spreading depressions, excitotoxicity and oxidative stress.

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## **KEY CONCEPTS UNDERLYING STROKE LOCALIZATION**

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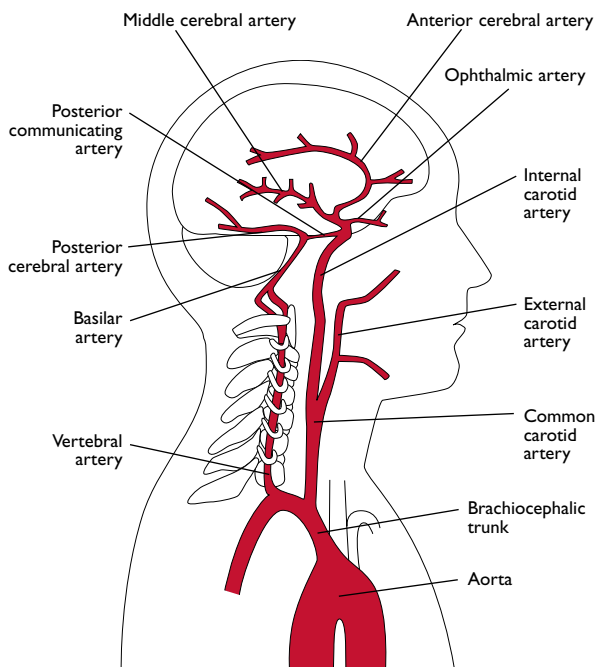
A fundamental understanding of cerebral arterial anatomy is critical for localizing lesions and selecting appropriate therapies. With the widespread use of neuroimaging in acute stroke evaluation, the conventional wisdom and rules of thumb used in stroke localization

have been refined. Furthermore, the limitations of lesion localization by neurologic examination and history alone have been revealed. This limitation is likely due to 3 factors. First, there is inherent variability in the distribution of vascular territories between individuals. Second, many of the systems tested (corticospinal for many motor functions, spinothalamic for many sensory functions) engage neural circuitry that passes through several arterial territories between cortex, basal ganglia, brainstem, and spinal cord. Finally, the penumbra effect creates situations in which large vascular lesions mimic smaller ones. Despite these complicating factors, large-vessel occlusions typically produce ischemia in a large territory, with resulting neurologic deficits in multiple domains. Small-vessel occlusions often produce lacunar syndromes, which are discussed in more detail below. Brainstem strokes cause characteristic ipsilateral cranial nerve and contralateral body deficits.

Among the many diagnostic tricks and rules of thumb, 2 groups of findings emerge as consistently useful: deficits in cortically based functions and deficits in brainstem-localizing functions. Cortically based functions are neurologic processes whose functions are mediated nearly exclusively through predictable areas of cerebral cortex. Most of these functions are from unimodal or multimodal association cortex. For example, expressive language and receptive language function localizes to the posterior-inferior frontal and posterior-superior temporal lobes, respectively. Other cortical localizing findings include cortical sensory deficits due to dysfunction of sensory association cortex (agraphesthesia, astereognosis), ideomotor apraxia, agnosias, hemiattention, and certain patterns of visual field defects. Of note, proper testing of integrative cortical functions requires the primary modality to be intact. For example, graphesthesia cannot be assessed in a patient with no touch sensation. Brainstem-localizing functions include certain patterns of oculomotor dysfunction or crossed deficits (facial and body sensory or motor deficits on opposite sides). Weakness affecting the brow as well as the lower face suggests an ipsilateral pontine lesion affecting the facial nucleus or nerve.

## **CEREBRAL ARTERIAL ANATOMY**

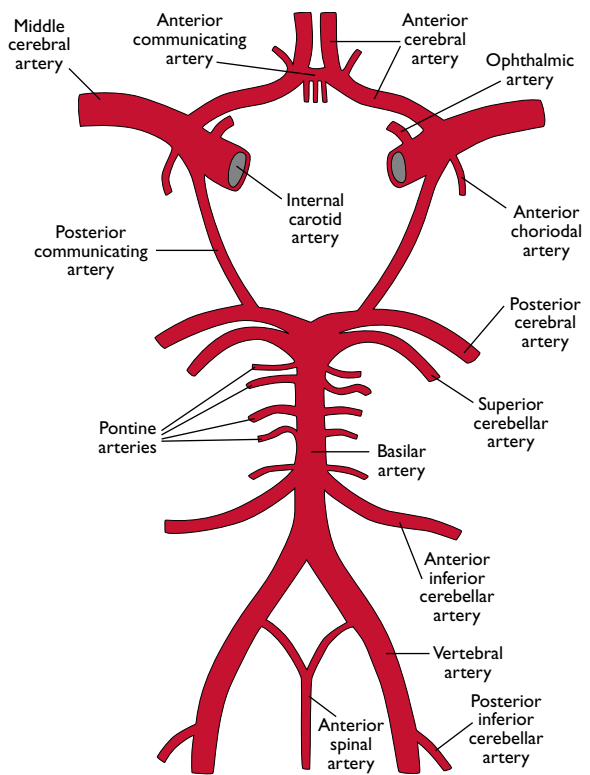
The aortic arch is the origin of all cerebral blood supply. Although many normal variants of arterial structure exist, **Figure 1** shows the standard anatomy of the extracranial and intracranial arteries. The circle of Willis is the arterial structure that connects the left, right, anterior, and posterior circulations (**Figure 2**). The anatomy of the circle of Willis is highly variable, with segments absent or hypoplastic in 55% of cases.<sup>45</sup>



**Figure 1.** The major arteries to the right side of the brain are shown in lateral view. The left-sided arteries follow the same pattern, with the exception that the left carotid artery branches directly from the aorta. (Adapted with permission from Porter R, editor. Merck manual of diagnosis and therapy. 18th ed. Whitehouse Station [NJ]: Merck; 2007:1790. Copyright 2007 Merck & Co., Inc.)

An anatomically based standardized nomenclature has been applied to segments of several of the major extra- and intracranial arteries (Table 4). The vessel segments have become a standard of communication among cerebrovascular surgeons, neuroradiologists, and neurologists. The nomenclature incorporates important vascular features, such as whether the vessel is intradural or extradural, which may have substantial ramifications in terms of therapeutic options or risk assessment for conditions such as aneurysm. Figure 3 and Figure 4 show important landmarks of the internal carotid and vertebral artery segments.

The brainstem receives its blood supply from many small penetrating arterioles that branch directly from the vertebral, basilar, and proximal cerebellar arteries. The main cerebellar arteries are the posterior inferior cerebellar arteries (which branch from the vertebral arteries) and the anterior inferior cerebellar arteries and superior cerebellar artery (which branch from the basilar artery). The main cerebral arteries are the anterior cerebral, middle cerebral, and posterior cerebral arteries. The anterior cerebral and middle cerebral arteries are products of the bifurcation of the



**Figure 2.** An inferior view of the circle of Willis. Blood enters the cerebral circulation through the vertebral and internal carotid arteries. The circle of anastomoses is formed by the C7 segment of the internal carotid arteries, the A1 segment of the anterior cerebral arteries, the anterior and posterior communicating arteries, and the P1 segment of the posterior cerebral arteries (see Table 4).

internal carotid arteries in the circle of Willis. The anterior cerebral artery has multiple cortical branches; the 4 most significant named branch arteries are listed in Table 4. The middle cerebral artery bifurcates into a superior and inferior trunk in 80% to 90% of cases, with trifurcation yielding an addition intermediate trunk in approximately 10% of cases and multiple divisions in rare instances.<sup>46-48</sup>

The anterior choroidal arteries are a separate branch of the internal carotid arteries. The posterior cerebral arteries are the products of the bifurcation of the basilar artery.

#### **ARTERIAL TERRITORIES AND STROKE SYNDROMES**

The major cerebral and cerebellar arteries deliver blood flow in a predictable distribution, which results in a pattern of consistent territories dependent on flow from particular arteries with interposing watershed regions that receive flow from 2 or more sources. As is the case with the anatomy of arterial branching,

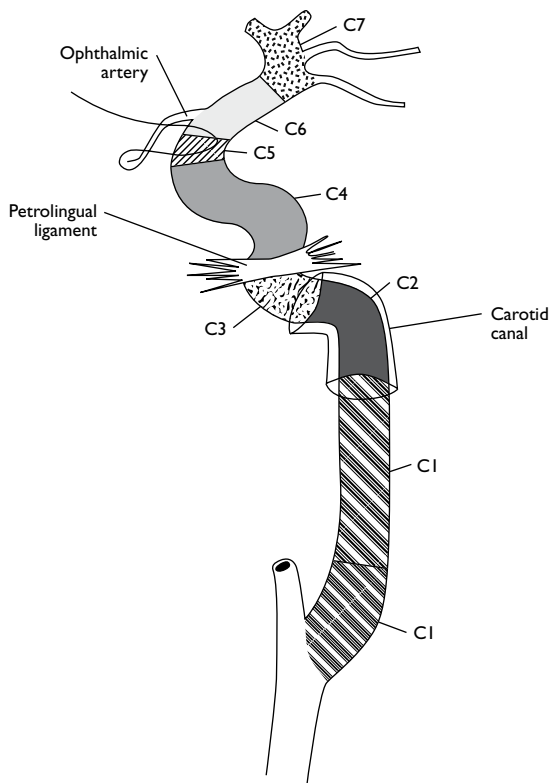
**Table 4.** Segments and Branches of the Major Arteries of the Cerebral Circulation

Vessel	Segment	Name	Anatomic Description	Important Segmental Branch Arteries
ICA	C1	Cervical	Carotid bifurcation to carotid canal at skull base	
	C2	Petrous	In petrous part of temporal bone	
	C3	Lacerum	Foramen lacerum to petrolingual ligament	
		<i>Petrous portion</i>	<i>C2 and C3 segments</i>	
	C4	Cavernous	Petrolingual ligament through the cavernous sinus to the proximal dural ring	
	C5	Clinoid	Short segment between proximal dural ring and distal dural ring	
	C6	Ophthalmic	Distal dural ring to the PComA	
C7		Communicating (or terminal)	PComA to the bifurcation into ACA and MCA	Anterior choroidal ACA MCA
		<i>Supraclinoid portion</i>	<i>C6 and C7 segments</i>	
VA	V1		Subclavian artery to transverse foramen of C5 or C6	
	V2		Inside transverse foramina from C5 or C6 to C2	
	V3	Tortuous	Transverse foramen of C2, looping posterolaterally around the arch of C1 and between atlas and occiput	
	V4	Intracranial	Entering dura at foramen magnum to formation of basilar artery	
ACA	A1		Origin from ICA to AComA	Medial lenticulostriates
	A2		AComA to rostrum of the corpus callosum	Recurrent artery of Heubner
	Cortical branches	Orbitofrontal	1st branch	
		Frontopolar	2nd branch	
		Callosomarginal	Largest branch	
Pericallosal		Final large branch (runs along top of corpus callosum)		
MCA	M1	Sphenoidal	Origin from ICA to bifurcation/trifurcation	Lenticulostriates, superior and inferior trunks
	M2	Insular	Branches of M1 from the bifurcation/trifurcation to circular sulcus of the insula	
	M3	Opercular	Branches of M2 segments from the circular sulcus of the insula to the surface of the sylvian fissure	
	M4	Cortical	Cortical branches	
	M5	Terminal	Distal extensions of the M4 segments	
PCA	P1		Basilar artery to PComA	Thalamoperforates
	P2		PComA to lateral posterior choroidal artery	Lateral posterior choroidal Thalamogeniculate
	P3 and P4	Cortical	Distal cortical branches	

ACA = anterior cerebral artery; AComA = anterior communicating artery; ICA = internal carotid artery; MCA = middle cerebral artery; PCA = posterior cerebral artery; PComA = posterior communicating artery; VA = vertebral artery

the distribution of flow territories shows minor variability within a generally consistent pattern. Careful anatomic studies have produced excellent topographic maps of major arterial territories, which serve as useful

clinical references.<sup>49–53</sup> **Figure 5** and **Figure 6** illustrate the distribution of the major cerebral and cerebellar arteries and identify important structures within their distribution. In the following section, arterial territories



**Figure 3.** Anatomic diagram of the internal carotid artery showing the 7 named segments (see Table 4), with important structural landmarks. (Adapted with permission from Osborn AG. *Diagnostic cerebral angiography*. 2nd ed. Philadelphia: Lippincott, Williams & Wilkins; 1999:58.)

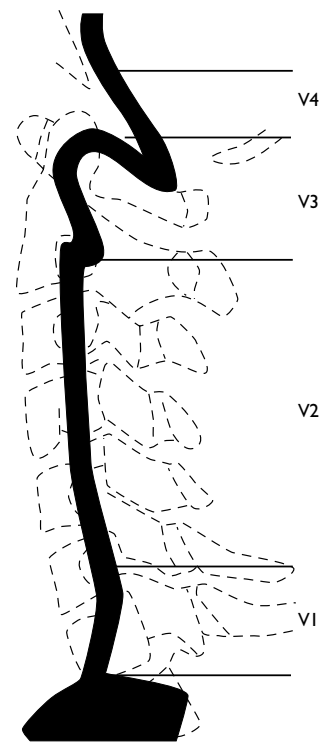
will be reviewed in more detail, along with the stroke syndromes attributable to them (Table 5).

### Anterior Cerebral Artery Syndromes

In general, the anterior cerebral artery supplies the medial portion of the frontal and parietal lobes. Infarction of this territory causes a contralateral hemianesthesia, as well as a hemiparesis that affects the leg much more than the arm or face due to the topography of the homunculus. Furthermore, damage to the medial frontal lobe impairs the behavioral executive function of the frontal lobes and can cause abulia. Dominant hemisphere anterior cerebral artery infarcts may produce mutism, and nondominant hemisphere infarcts may produce an acute confusional state. Severe abulia in the form of akinetic mutism is usually seen only in bilateral anterior cerebral artery infarcts, along with urinary incontinence.

### Middle Cerebral Artery Syndromes

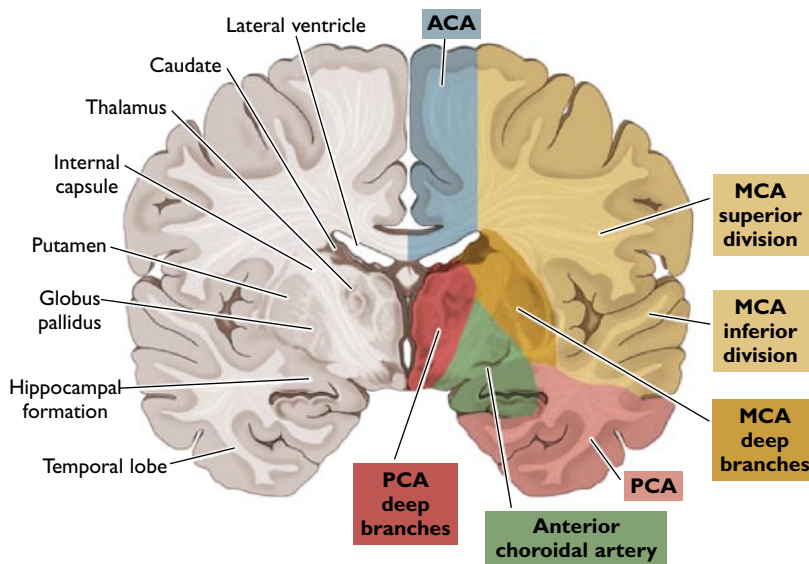
The middle cerebral artery supplies the remainder of



**Figure 4.** Anatomic diagram of the vertebral artery showing the 4 named segments (see Table 4), with important structural landmarks. (Adapted with permission from Shin JH, Suh DC, Choi CG, Leei HK. *Vertebral artery dissection: spectrum of imaging findings with emphasis on angiography and correlation with clinical presentation*. *RadioGraphics* 2000;20:1688. Copyright 2000 Radiological Society of North America.)

the frontal and parietal lobes, as well as the superior portion of the temporal lobe. Strokes affecting the complete territory lead to contralateral hemiparesis, hemianesthesia, and hemianopia. Loss of attention-related frontal lobe functions causes a hemineglect syndrome with an ipsilateral gaze preference. Language impairment occurs in dominant middle cerebral artery lesions, manifesting as expressive aphasia from lesions to Broca's area in the posterior-inferior frontal lobe and as receptive aphasia from lesions to Wernicke's area in the posterior-superior temporal lobe. Damage to the corresponding areas in the nondominant hemisphere causes more subtle symptoms of language impairment in the form of expressive (motor) and receptive (sensory) aprosodia.

In complete proximal middle cerebral artery occlusions, there is duplicative damage to sensory, motor, language, and executive functions via damage to both the cortical representations and basal ganglia circuit structures. Lesions of the middle cerebral artery in the distal M1 segment or at the bifurcation can leave blood



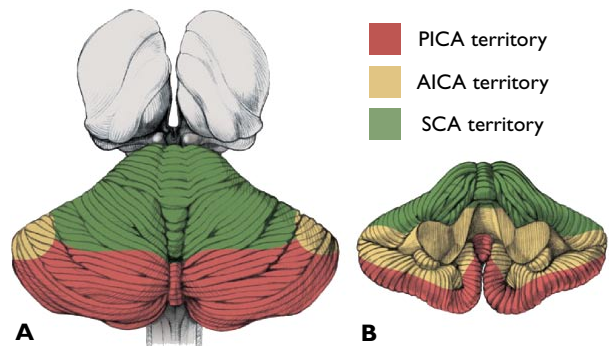
**Figure 5.** Coronal diagram showing the major vascular territories of the brain and important anatomic structures. ACA = anterior cerebral artery; MCA = middle cerebral artery; PCA = posterior cerebral artery. (Adapted with permission from Blumenfeld HJ. *Neuroanatomy through clinical cases*. Sunderland [MA]: Sinauer Associates; 2002:375.)

flow to the lenticulostriate arteries unimpeded, sparing the basal ganglia and internal capsule. In this context, the pattern of sensory and motor deficits may be irregular and incomplete, especially sparing leg function due to the topography of the homunculus previously described.

Occlusion of the superior division of the middle cerebral artery leads to a syndrome of predominantly frontal dysfunction, with prominent motor and expressive language deficits with variable sensory loss. In contrast, inferior division middle cerebral artery strokes create prominent hemianopsia and receptive language deficits. One rare but well-described cluster of deficits from dominant hemisphere temporoparietal (angular gyrus area) stroke is Gerstmann syndrome, which consists of agraphia, acalculia, right-left confusion, and finger agnosia.

### Posterior Cerebral Artery Syndromes

The posterior cerebral artery supplies the inferior temporal lobe and occipital lobe. Lesions in the posterior cerebral artery that spare early arterial branches to deep structures cause contralateral homonymous hemianopsia. Lesions of the dominant hemisphere can create the interesting phenomenon of alexia without agraphia, in which reading function is impeded by the combination of a unilateral visual field defect and an impaired connection between the contralateral intact visual field and receptive language area of the dominant hemisphere due to infarction of the fiber tracts projecting posteriorly through the splenium of the corpus callosum. Bilateral occipital lobe damage



**Figure 6.** Posterior view (A) and anterior (with brainstem removed) view (B) of the cerebellum showing the major vascular territories. AICA = anterior inferior cerebellar artery; PICA = posterior inferior cerebellar artery; SCA = superior cerebellar artery. (Adapted with permission from Blumenfeld HJ. *Neuroanatomy through clinical cases*. Sunderland [MA]: Sinauer Associates; 2002: 656.)

can lead to cortical blindness with denial of deficits and confabulation (Anton syndrome). More extensive bilateral posterior cerebral artery infarctions affecting the posterior parietal lobes cause oculomotor apraxia (difficulty directing gaze to a point of interest), optic ataxia (difficulty visually guiding limb movements), and simultagnosia (inability to recognize an integrated visual presentation from its multiple compositional elements), a condition known as Balint syndrome.

### Syndromes Involving Arteries to Deep Cerebral Structures

All 3 cerebral arteries, the anterior and posterior communicating arteries, and the anterior choroidal

## *Ischemic Stroke: Pathophysiology and Localization*

**Table 5.** Stroke Syndromes

Syndrome	Localization	Symptoms
<b>Major Cerebral Artery Syndromes</b>		
Anterior cerebral artery	Median frontoparietal	Contralateral anesthesia, leg > arm hemiparesis, abulia; dominant hemisphere: mutism; nondominant hemisphere: acute confusional state; bilateral infarction: urinary incontinence, akinetic mutism
Middle cerebral artery, complete	Lateral frontoparietal, superior temporal	Contralateral hemianesthesia, hemiparesis, hemianopia with gaze preference; dominant hemisphere: aphasia and apraxia; nondominant hemisphere: aprosodia, hemineglect
Middle cerebral artery, superior division	Lateral frontal	Contralateral hemiparesis, expressive aphasia
Middle cerebral artery, inferior division	Lateral parietal and superior temporal	Contralateral hemianopia, receptive aphasia
Gerstmann	Dominant hemisphere angular gyrus area	Agraphia, acalculia, right-left confusion, finger agnosia, ideomotor apraxia
Distal posterior cerebral artery	Inferior temporal and occipital	Hemianopia
Alexia without agraphia	Dominant occipital lobe and splenium of corpus callosum	Alexia without agraphia
Anton	Bilateral occipital	Cortical blindness with denial of deficit
Balint	Bilateral parieto-occipital	Oculomotor apraxia, optic ataxia, simultagnosia
Recurrent artery of Heubner	Head of caudate and anterior limb of internal capsule	Contralateral face and arm weakness, motor aphasia
Anterior choroidal artery	Posterior limb of internal capsule, posterior corona radiata	Contralateral hemiparesis (severe), hemianesthesia, hemianopia (uncommonly)
<b>Lacunar Syndromes</b>		
Pure motor	Posterior limb of internal capsule or thalamus	Contralateral hemiparesis
Sensorimotor	Posterior limb of internal capsule or thalamus	Contralateral hemiparesis, hemisensory loss
Pure sensory	Posterior limb of internal capsule or thalamus	Contralateral hemisensory loss
Dejerine-Roussy	Thalamus	Contralateral hemisensory loss with hemibody pain
Hemiballismus	Subthalamic nucleus	Contralateral hemiballismus
Ataxic hemiparesis	Corona radiata, internal capsule, basal ganglia, or pons	Contralateral hemiparesis with prominent ataxia
Dysarthria-clumsy hand	Corona radiata, internal capsule, basal ganglia, or pons	Contralateral dysarthria and upper limb ataxia
<b>Brainstem Syndromes</b>		
Weber	Cerebral peduncle and ventral midbrain (sparing red nucleus and cerebellothalamic tract)	Ipsilateral oculomotor palsy, contralateral body weakness
Claude	Ventral midbrain and superior cerebellar peduncle (near red nucleus)	Ipsilateral oculomotor palsy, contralateral tremor
Benedikt	Cerebral peduncle and ventral midbrain (including red nucleus and cerebellothalamic tract)	Ipsilateral oculomotor palsy, contralateral body weakness and tremor
Locked-in	Bilateral median pontine	Quadriplegia with bulbar plegia sparing some eye movements
Marie-Foix	Lateral pons	Ipsilateral ataxia, contralateral weakness and loss of pain and temperature
Raymond	Ventral pons	Ipsilateral abducens palsy, contralateral hemiparesis
Millard-Gubler	Mid pons	Ipsilateral facial weakness, contralateral body weakness
Foville	Dorsal pons	Ipsilateral lateral gaze palsy and facial weakness
Dejerine	Medial medulla	Ipsilateral tongue weakness, contralateral hemiparesis and loss of vibration and proprioception
Wallenberg	Lateral medulla	Ipsilateral facial sensory loss, Horner's syndrome, palatal weakness, dysphagia and ataxia, contralateral body pain and temperature loss

arteries have branches that supply the basal ganglia and limbic structures. The deep structures of the brain are supplied by clusters of small penetrating arteries named for the structures they supply. The lenticulostriate arteries supply the putamen, globus pallidus, internal capsule, and caudate head (*lentiform nucleus* = putamen and globus pallidus; *striatum* = caudate and putamen and area of striated fibers bridging them.) The medial lenticulostriate arteries branch from the anterior cerebral artery, and the lateral lenticulostriate arteries branch from the middle cerebral artery.<sup>54</sup> The recurrent artery of Heubner is a large medial lenticulostriate artery arising from the anterior cerebral artery near the junction with the anterior communicating artery. This artery is prone to damage during aneurysm clipping, leading to infarcts of the head of the caudate and anterior limb of the internal capsule.<sup>55</sup> Occlusion of this vessel may lead to weakness of the face and arm with dysarthria as well as a motor aphasia.

The anterior choroidal artery, a direct branch of the distal internal carotid artery, supplies the posterior limb of the internal capsule, posterior paraventricular corona radiata, a segment of the optic tract, and the choroid plexus of the lateral ventricle. The anterior hippocampus and parahippocampus may also derive blood supply from this vessel. Infarcts of this small artery can lead to a classic triad of severe hemiplegia, hemianesthesia, and hemianopia that mimics a complete middle cerebral artery infarct, although hemianopia is rare.<sup>56,57</sup>

The remaining posterior aspects of the internal capsule and optic tracts are supplied by the anterior thalamoperforating arteries that branch off the posterior communicating arteries. In addition to deriving blood from the anterior thalamoperforating arteries, the thalamus and its lateral geniculate nucleus receive blood supply from the posterior thalamoperforating and thalamogeniculate arteries that branch from the posterior cerebral artery. The other deep penetrating branches of the posterior cerebral artery include the medial and lateral posterior choroidal arteries, which supply the quadrigeminal plate and pineal gland as well as portions of the posterior thalamus, hippocampus, and parahippocampus.

### **Lacunar Syndromes**

Infarcts of the small penetrating arteries to deep structures can damage communicating white matter tracts or deep nuclear structures involved in functional circuits with overlying cortex, mimicking discrete cortical lesions. Although many combinations of deficits can be observed, several classic lacunar syndromes have been described. Many of these syndromes present as

a dense deficit in one modality without symptoms in other modalities controlled by cortical regions in the same major artery watershed (ie, profound weakness without sensory deficits, or profound right weakness and sensory loss without aphasia). Pure motor hemiparesis, pure sensory stroke, and sensorimotor stroke can result from small infarcts to the posterior limb of the internal capsule or thalamus. These syndromes all lack language or visual impairment. Some pure sensory strokes due to thalamic lacunes can cause a central hemibody pain syndrome (Dejerine-Roussy syndrome). Ataxic hemiparesis (weakness with incoordination out of proportion to the weakness) and the dysarthria-clumsy hand syndrome have been observed due to lesions in the corona radiata, internal capsule, basal ganglia, and pons. Finally, lesions directly to basal ganglia structures can produce extrapyramidal movement disorders. Hemiballismus has been linked to lesions of the contralateral subthalamic nucleus, dystonia and chorea to the lentiform nucleus, and a coarse, slow “rubral” tremor with lesions near the red nucleus.

### **Brainstem Syndromes**

The brainstem is supplied by penetrating arterioles from the vertebral and basilar arteries, as well as from vessels originating from the most proximal portions of the cerebellar arteries. The cerebellum is supplied as the artery names suggest: the most inferior and posterior portion by the posterior inferior cerebellar artery, the anterolateral portion by the anterior inferior cerebellar artery, and the superior portion by the superior cerebellar artery. There are several well-described infratentorial stroke syndromes. In the cerebellum, strokes affecting the superior vermis cause gait dysfunction, and damage to the inferior vermis leads to truncal instability. Lesions to the cerebellar hemispheres or deep cerebellar nuclei cause ipsilateral limb ataxia and nystagmus.

The brainstem contains many important tracts and nuclei, so slight variability in the extent of infarctions in the same region can lead to significant variations in symptoms. Nevertheless, a solid understanding of brainstem neuroanatomy can often facilitate localization. A key principle is that tracts traversing the brainstem between the brain and spinal cord carry signals to the contralateral body, but all nuclei other than the trochlear nerve nuclei subserve ipsilateral structures. Therefore, lesions affecting both tracts and nuclei can lead to crossed body findings such as weakness in the left face and right arm and leg. Penetrating branches to the midbrain can cause ipsilateral oculomotor gaze palsy in conjunction with contralateral body weakness (Weber syndrome), tremulous ataxia (Claude

syndrome), or body weakness and tremulous ataxia (Benedikt syndrome) as the oculomotor fibers, corticospinal tract, red nucleus, and cerebellothalamic tract are affected from the ventral cerebral peduncles moving dorsally.<sup>58</sup> Upgaze and convergence palsy from dysfunction of the dorsal midbrain (Parinaud syndrome) is more frequently caused by extra-axial compression than by stroke.

Bilateral medial pontine lesions can produce a locked-in state with quadriplegia and nearly complete bulbar plegia, but eye movements other than lateral gaze are usually spared. Stroke in the lateral pons leads to ipsilateral ataxia, contralateral spinothalamic deficits, and contralateral weakness (Marie-Foix syndrome). Lesions of the ventral pons interrupt the corticospinal tract, causing contralateral body weakness along with ipsilateral abduction palsy due to involvement of the exiting abducens fibers (Raymond syndrome). Mid-pontine lesions affect the facial nerve nucleus as well as the descending corticospinal tract, also leading to ipsilateral facial and contralateral body weakness (Millard-Gubler syndrome). Lesions of the dorsal pons affect the abducens and facial nuclei, causing ipsilateral lateral gaze palsy and facial weakness (Foville syndrome). Infarction of the medial medulla leads to ipsilateral tongue weakness, with contralateral disruption of the corticospinal tract leading to hemiparesis and disruption of the medial lemniscus causing vibration and proprioception deficits (Dejerine syndrome). The lateral medullary syndrome (Wallenberg syndrome) consists of ipsilateral face and contralateral body pain and temperature loss, ipsilateral Horner syndrome, ipsilateral ataxia, and hoarse voice with dysphagia.<sup>59</sup>

### **Watersheds and Collaterals**

Although most ischemic strokes occur within the cores of vascular territories as a result of transient or permanent arterial obstruction (focal hypoperfusion), the watershed regions most distal from the main source arteries are particularly susceptible to global hypoperfusion. Global hypoperfusion to cerebral arteries has many causes, including systemic hypotension, especially in patients with significant carotid stenosis. Watershed strokes appear as small, irregular infarcts distributed along the border of vascular territories and have been described as having a radiographic appearance of a string of beads or pearls. Recognition of this infarct location and pattern is useful in clarifying stroke etiology and in guiding potential interventions to improve flow dynamics or prevent recurrent systemic hypotension.

Redundant arterial supply protects neuronal tissue, which is much more intolerant to ischemia than most

other body tissues. Collateral arterial channels exist both within the intracranial circulation and between the extracranial and intracranial circulations. The most important intracranial collateral channels are the anterior and posterior communicating arteries that complete the circle of Willis. Furthermore, anastomoses are present between distal cortical branches of the major cerebral arteries. Several collateral channels bridge the extracranial and intracranial circulations. The most important collateral channels are located between the facial, maxillary, and middle meningeal arteries from the external carotid circulation to the ophthalmic artery, a branch of the internal carotid, and from the middle meningeal and occipital arteries to the cortical cerebral artery branches.<sup>60</sup>

Extracranial to intracranial collaterals may become the primary source of blood flow in certain conditions that cause stenosis of proximal intracranial vessels. In such cases, when naturally occurring collateral vasculature becomes insufficient, a few surgical options exist that may enhance collateral circulation. These surgical procedures will be discussed in the second half of this review.

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### **SUMMARY**

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As the third leading cause of death in the United States,<sup>1</sup> the impact of stroke cannot be overstated. A full understanding of the pathogenetic mechanisms of ischemic stroke and principles of stroke localization are fundamental to the practice of neurology. Emerging neuroprotective therapies are being designed to interrupt various steps of the apoptotic process in neurons. Implementing these treatments into clinical practice will require familiarity with applied principles of the cellular pathophysiology reviewed here. Although most ischemic strokes are due to atherosclerosis-related arterial thrombosis or cardioembolism, familiarity with other less common mechanisms such as vasculitis and genetic syndromes is critical for accurate diagnosis and appropriate treatment. Finally, the localization of most strokes can be determined through knowledge of vascular anatomy and recognition of common stroke syndromes, and the presenting syndromes often suggest the underlying etiology of the lesion.

#### **BOARD REVIEW QUESTIONS**

Test your knowledge of this topic. Go to [www.turner-white.com](http://www.turner-white.com) and select Neurology from the drop-down menu of specialties.

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