Diagnosis of Ischemic Stroke

Series Editor and Contributor:
Steven K. Feske, MD
Assistant Professor of Neurology
Harvard Medical School
Director, Stroke Division
Department of Neurology
Brigham and Women’s Hospital
Boston, MA

Table of Contents

Introduction .................................................. 2
Organizing Principles ........................................ 2
Embolic Stroke ................................................ 2
Large Vessel Disease ......................................... 7
Small Vessel Disease ......................................... 9
Uncommon Stroke Diagnoses ............................. 10
Case Presentations .......................................... 11
Summary Points ............................................. 14
References .................................................. 14

Cover Illustration by Craig Zuckerman
I. **INTRODUCTION**

Stroke is the third leading cause of death in the United States. Approximately 150,000 patients die from stroke each year, and about 600,000 are left with disabilities. It is the most common neurologic diagnosis prompting hospital admission and the disease on which the understanding of topographic neurologic localization in the central nervous system is largely based. Accurate clinical diagnosis of patients with ischemic stroke is based on an understanding of basic neuroanatomy, cerebrovascular anatomy, and the pathophysiologic mechanisms by which vascular occlusions and ischemia can occur.

This article provides an organized approach to the diagnosis of ischemic stroke. The focus is on the clinical diagnosis of stroke syndromes along with the application of imaging and laboratory testing to establish a clear understanding of the pathophysiology that underpins the proper application of available therapies. Five case patients are presented to illustrate essential features of the diagnosis of stroke. Subsequent articles for Volume 7 will address acute therapy and prevention.

II. **ORGANIZING PRINCIPLES**

When assessing a patient with acute ischemic stroke, the goal is to establish quickly whether a stroke has occurred and to determine the vascular distribution, disease mechanism, and expected time course of its evolution. Using this information, the physician can plan optimal diagnostic evaluation and therapy.

**TOPOGRAPHIC AND VASCULAR LOCALIZATION**

Principles of classic clinical neurologic localization allow the physician to correlate particular neurologic deficits with specific lobes and deep structures. It is then possible to conclude that a focal deficit is present and to draw conclusions about its pathogenesis. Based on the localization, extent, and character of a deficit, it is possible to narrow the possible sites of vascular occlusion or stenosis. This vascular localization allows an imaging evaluation to be designed that demonstrates the vascular lesion in many cases.

**PATHOPHYSIOLOGIC MECHANISMS CAUSING STROKE**

With the knowledge of the vascular lesion and additional clues drawn from the nature of the underlying disease and time course, the pathophysiologic mechanism by which the stroke occurred can be inferred. Major mechanisms include embolism, large vessel stenosis, occlusion with compromised flow or embolism, and small vessel stenosis or occlusion. These categories are overlapping; they can be further refined and elaborated.

**TIME COURSE**

In most cases, the operational definition of acute ischemic stroke depends on the description of the onset of the event as sudden. Acute ischemic stroke can be further categorized as transient ischemic attack (TIA), completed stroke, and stroke-in-evolution; these categories have evolved in recent years with the added knowledge conveyed by modern neuroimaging. Although often difficult to establish at the point of contact, it remains important to establish the expected early future development of a stroke when planning therapy and its pace.

III. **EMBOLIC STROKE**

**ANTERIOR CIRCULATION**

The middle cerebral artery (MCA) supplies the motor and sensory cortex for the face and upper extremity in the frontal and parietal lobes; the deep white matter from the lower extremities’ cortical territory in the anterior cerebral artery (ACA) field; the frontal eye fields in the frontal cortex; and the temporal and parietal optic radiations. On the left, the major language areas in the frontal (Broca’s area) and temporal (Wernicke’s area) lobes and, on the right, the frontal and parietal centers for directed attention are supplied by the MCA. Arising from the proximal stem...
of the MCA, the penetrating lenticulostriate vessels supply the basal ganglia and internal capsule. The anterior choroidal artery usually arises from the suprachoroidal internal carotid artery (ICA) just after the posterior communicating artery. The anterior choroidal artery supplies a portion of the posterior limb of the internal capsule, adjacent optic radiations, and a small portion of the thalamus (including the lateral part of the lateral geniculate body).

The ACA supplies the major motor and sensory cortex for the lower extremity in the medial and paramedian frontal and parietal lobes; the cingulate gyrus; on the left, the supplementary motor area on the medial frontal lobe; and the anterior corpus callosum. The recurrent artery of Heubner branches from the proximal ACA and proceeds posteriorly to supply a portion of the head of the caudate nucleus and a portion of the anterior limb of the internal capsule and adjacent structures.

The Full MCA Syndrome

Sudden occlusion of the MCA stem typically causes hemiplegia, forced conjugate gaze deviation to the side of the ischemic lesion, and homonymous hemianopia. In addition, patients have aphasia if occlusion occurs on the left; they have hemi-neglect and anosognosia if occlusion occurs on the right. However, the actual symptoms seen in a given patient depend on the status of collateral circulation. Various partial syndromes may occur. Occlusion of the MCA stem in patients with good collateralization of cortical vessels via flow from the ACA, posterior cerebral artery (PCA), and external carotid artery (ECA) will often cause a large infarction in the deep perfusion field of the lenticulostriate vessels affecting the basal ganglia and internal capsule. This infarction may cause a pure motor hemiplegia that mimics the typical lacunar syndrome seen with small vessel disease (so-called Gerstmann’s syndrome!!) suggest occlusion of a posterior division branch to these sites. Branch or division occlusions are suggested by Broca’s, Wernicke’s, and many transcortical aphasias. Quadrantanopias suggest temporal (superior quadrantanopia) or parietal lesions (inferior quadrantanopia).

Anterior Choroidal Artery Syndrome

Anterior choroidal artery occlusion typically causes hemiplegia and hemisensory loss, without cortical features and hemianopia. This last is variable, but the quadruple-sectoranopia, hemianopia sparing the horizontal meridian, is considered diagnostic. This syndrome is caused by infarction of the inferior lateral geniculate nucleus.

ACA Syndrome

Occlusion of the ACA causes contralateral lower extremity weakness and sensory loss. Lesions of the left supplementary motor area may cause muteness or transcortical motor aphasia (nonfluent with repetition sparing). Lesions of the cingulate gyrus may cause extreme abulia (akinetic mutism), especially bilateral lesions, which can occur when the ACAs have a common origin or supply.

Carotid T Syndrome

A more proximal anterior circulation embolic occlusion may occur when an embolism lodges at the carotid bifurcation. This occlusion usually causes a large deficit combining the MCA and ACA syndromes, again with variations based on the idiosyncrasies of the collateral circulatory supply.

POSTERIOR CIRCULATION

The PCAs arise from the terminal bifurcation of the basilar artery (BA) to supply the occipital lobe (including the primary visual cortex and the posterior corpus callosum) and to supply the inferior and medial temporal lobes (including the hippocampi). In 10% to 15% of individuals, the fetal pattern of flow persists with the main supply of the PCA coming from the anterior circulation via a large posterior communicating artery while the first segment of the PCA (connecting the BA and more distal PCA) is hypoplastic.

Occlusion of the PCA causes homonymous hemianopia often sparing macular vision or quadrantanopia if only one bank of the calcarine fissure is affected, memory loss, and visual agnosias because of inferior temporoparietal lesions (eg, prosopagnosia, color agnosia [inability to identify colors], achromatopsia [inability to sort by color categories]), especially when bilateral. Left
occipital infarction that extends to the splenium of the corpus callosum may cause alexia without agraphia.\textsuperscript{9} In addition, penetrating arteries arising from the proximal PCAs supply most of the thalamus; therefore, infarctions in the PCA territory are often accompanied by thalamic lesions.

The BA arises from the confluence of the 2 vertebral arteries and tapers slightly towards its distal tip. From the distal BA and the proximal PCAs arise the penetrating arteries to the thalamus, midbrain, and superior cerebellar arteries (SCA). Emboli entering the BA often travel to its tip. The fully expressed “top of the basilar” syndrome comprises the following deficits (patients typically present with a variable subset of these deficits):\textsuperscript{10,11}

1. Decreased level of consciousness (ascending reticular activating system [RAS] in the upper pons and midbrain reticular formation);
2. Ptosis (levator palpebrae subnucleus in the midbrain tegmentum);
3. Supranuclear palsies of vertical gaze (upper medial midbrain centers for vertical gaze integration, posterior commissure);
4. Disconjugate gaze often including an ipsilateral hypertropic skew (oculomotor nucleus and nerve);
5. Pupillary abnormalities (cranial nerve 3 [CN III] and Edinger-Westphal nucleus);
6. Peduncular hallucinosis (upper midbrain);
7. Memory loss (medial temporal lobes);
8. Cortical visual loss and visual agnosias (occipital and ventral temporo-occipital lobes);
9. Hemiplegia or quadriplegia (corticospinal tracts in midbrain cerebral peduncles); and
10. Ataxia (cerebellum via SCA and superior cerebellar peduncles in the midbrain).\textsuperscript{10,11}

Less commonly, posterior circulation emboli lodge more proximally in the BA, especially when there is narrowing because of atheroma. Emboli that enter the vertebral arteries may also occlude the posterior inferior cerebellar artery (PICA) causing inferior cerebellar infarction. These infarctions usually spare the lateral medullary territory (see below), although it is sometimes affected.

**PATHOPHYSIOLOGIC MECHANISMS OF EMBOLISM**

**Cardioembolism**

Atrial fibrillation, valvular heart disease, myocardial infarction, and dilated cardiomyopathy all predispose to thrombus formation within the heart and to distal embolization. The added risk conveyed by mitral annular calcification and mitral valve prolapse is low.\textsuperscript{15} A history of intravenous drug abuse, infection, vascular access lines, systemic embolic phenomena, known valvular heart disease, valvular prosthesis, fever, and heart murmur should all raise the question of possible endocarditis in a patient presenting with stroke or TIA. Nonbacterial thrombotic endocarditis (NBTE, marantic endocarditis) may occur in the context of hypercoagulability from malignancy or inflammatory disorders, such as antiphospholipid antibody syndrome and systemic lupus erythematosus (Libman-Sacks endocarditis).\textsuperscript{13,14}

**Paradoxical Embolism**

An atrial septal communication, usually a patent foramen ovale (PFO), is a possible route for paradoxical arterial embolism from a venous source. Because PFO is so common (approximately 25\% of asymptomatic adults), physicians must be careful before concluding that a demonstrated lesion is relevant in a particular case.\textsuperscript{15,16} Comparison studies of populations with cryptogenic embolic stroke suggest that PFO and PFO with atrial septal aneurysm play a significant role in the pathogenesis of stroke.\textsuperscript{15–17} Other vascular shunts, such as pulmonary arteriovenous fistulas, may also serve as conduits for paradoxical embolism.

**Artery-to-Artery Embolism**

In many cases of stroke due to large vessel disease, the mechanism of infarction is embolic with the large artery atheroma or vascular dissection providing the source of the embolic material (Figure 1). Atherosclerosis of the aortic arch has been recognized as an important cause of embolism.\textsuperscript{18,19} As with PFO, this conclusion has been supported by population data on patients with cryptogenic embolic stroke; although this common lesion can be demonstrated easily, its implication in a particular instance of stroke is problematic.

**IMAGING AND LABORATORY EVALUATION**

The evaluation of patients with presumed embolic infarction includes: (1) the clinical definition of the stroke looking for characteristic patterns; (2) the demonstration by computed tomography (CT) or magnetic resonance imaging (MRI) of compatible infarctions; (3) the demonstration by CT angiography, magnetic resonance angiography (MRA), or conventional angiography of the site of embolic occlusion; and (4) a search for the source of the emboli and underlying risk factors.
CT scans usually do not show signs of infarction within the first few hours after onset of ischemic stroke, although subtle evidence of infarction can sometimes be seen early. A dense MCA sign refers to the visualization of radiodense thrombus in the MCA stem on noncontrast CT. Effacement of cortical sulci and loss of gray-white differentiation may be seen in the cortex and deep nuclei. Loss of gray-white differentiation in the subinsular region has been called the insular ribbon sign. More advanced infarction will cause frank hypodensities and

Figure 1. Artery-to-artery embolism. Non-contrast CT and CT angiogram of a 73-year-old right-handed man who presented 6 hours after sudden onset of aphasia, right hemianopia, and hemiplegia. (A) Non-contrast CT shows early signs of a large, left MCA territory infarction with loss of gray-white differentiation (white arrow shows this in the insula, insular ribbon sign) and sulcal effacement (black arrows). CT angiogram in the axial (B) and frontal (C) planes demonstrates the abrupt cut-off of the contrast column in the left MCA stem because of an occluding embolus (white arrow). The axial image also demonstrates the paucity of filling of the distal MCA branches (black arrows) when compared to the right side. (D) CT angiogram of the left cervical carotid arteries shows calcification in the area of the carotid bulb and severe narrowing at the origin of the left ICA (white arrow in lower right corner). The atherosclerotic plaque of the left proximal ICA is the presumed source of the left MCA embolus. CT = computed tomography; ICA = internal carotid artery; MCA = middle cerebral artery.
edema with mass effect. Secondary hemorrhage may be seen with the infarction on noncontrast CT.

MRI is more sensitive than CT for detection of early infarction. Diffusion-weighted imaging allows definition of the location and size of established infarction at presentation. Perfusion-weighted imaging allows definition of the area of hypoperfusion that may surround an established infarction. The combination of these techniques represents an approximate imaging demonstration of the ischemic core and penumbra of an evolving infarction. This information can be applied to decision making in patients with acute stroke, although time delay and availability still limit the usefulness of these techniques for acute decision making in most centers.

Vascular imaging by MRA or CT angiography is now widely available in the United States for noninvasive assessment of the intracranial vessels of the circle of Willis and of the cervical vessels. This list of areas for assessment can now be extended to include the aortic arch and the origin of the great vessels when needed. Both techniques now provide rapid direct demonstration of vascular occlusions in large and medium-sized arteries to guide decision making in patients with acute stroke. The benefits of increased information must be weighed against the time delays when thrombolytic therapies are being considered. However, in many centers, CT angiography can be added to the initial CT study with minimal added scanning time.

An electrocardiogram is important to establish the rhythm, especially to look for atrial fibrillation and for evidence of acute cardiac ischemia. Although of low yield statistically when specific lesions are not suspected, it is important to obtain extended cardiac rhythm monitoring by telemetry or Holter monitor and to perform echocardiography if a source of embolism is to be seriously sought. Transthoracic echocardiography (TTE) is insensitive; however, it is highly specific (ie, identified lesions are reliable, although negative studies are not reliable). Transesophageal echocardiography (TEE) cannot be routinely recommended; however, this sensitive study can be pursued if cardiac lesions, which might alter therapy, are suspected. TEE also allows good visualization of the ascending aorta and arch.

Blood cultures and echocardiography (TEE if TTE is nondiagnostic) should be done in any patient with fever, increased leukocyte count, heart murmur, valvular disease, valve prosthesis, evidence of systemic emboli (eg, splinter hemorrhages, Roth spots, Osler’s nodes, Janeway lesions) or a background suggesting high risk for endocarditis (such as a history of intravenous drug abuse, vascular instrumentation, or infections). Large vegetations can sometimes be identified on heart valves when there is no heart murmur and when TTE shows no lesions. Therefore, these insensitive tests cannot be relied on for diagnosis. Erythrocyte sedimentation rate (ESR), C-reactive protein, and rheumatoid factor are usually increased in endocarditis although they are nonspecific.

When paradoxical embolism is considered, a search is made for (1) a venous-to-arterial communication, usually a PFO (also consider possible pulmonary arteriovenous fistula) and (2) an embolic source in the venous circulation, such as lower extremity deep vein thrombosis. A MR venogram for pelvic venous thrombosis may be revealing in some otherwise negative cases.

It is common practice to perform a “hypercoagulability workup” in many patients with embolic disease. Proper application of the numerous tests has not been defined, and the tests should be applied selectively. Malignancy is a major cause of hypercoagulability and should be sought in patients with nonbacterial thrombotic endocarditis and other unexplained embolism. Adenocarcinoma of the colon, lung, breast, and pancreas are the most likely causes of systemic hypercoagulability with arterial manifestations—often because of NBTE. In such patients, the following studies are appropriate: measurement of hemoglobin, hematocrit, and mean corpuscular volume; assessment of stool for occult blood; colonoscopy; chest radiography; CT scanning of the chest, abdomen, and pelvis; and mammography. Such patients are not likely to have the protein deficiencies or autoantibodies that are often sought in a hypercoagulability workup. In many cases, they will have subtle abnormalities of the coagulation studies reflecting activation of the thrombin generation and fibrinolytic systems (eg, increased D-dimer or fibrin degradation products). Occasionally, frank disseminated intravascular coagulation with fibrinogen and platelet consumption, increased international normalized ratio (INR), and prolonged partial thromboplastin time (aPTT) are found.

Antiphospholipid antibody syndrome also causes arterial events often with NBTE involving the mitral valve. Decreased platelet levels and a history of second-trimester miscarriages in women should raise suspicion for this syndrome. Patients may have false-positive antinuclear antibodies, false-positive Reiter protein reagin (RPR), and false-positive Lyme serologies. Activated partial thromboplastin time (aPTT) is the most likely of the common screening coagulation tests to be abnormal, although it usually is not. Anticardiolipin antibodies are increased in most patients. High specificity depends on a
high titer (> 80 GPL unit for IgG). A “lupus anticoagulant” may be found by functional tests of the clotting system (eg, sensitive PTT, platelet neutralization test, Russell’s viper venom). Because the anticardiolipin antibody and lupus anticoagulant tests are discordant and neither is highly sensitive, it is best to obtain both when seeking to confirm a diagnosis of antiphospholipid antibody syndrome. Other autoantibodies have been associated with this clinical syndrome and can be assessed when the anticardiolipin antibody and lupus anticoagulant tests are negative despite a suggestive presentation. These autoantibodies include anti-prothrombin antibodies and anti-β-2-glycoprotein antibodies. Heparin-induced thrombocytopenia (HIT) is an iatrogenic, acquired coagulopathy; HIT antibodies can be assessed in the clinical setting of heparin exposure.

Inherited and acquired deficiencies of protein C, protein S, antithrombin III, factor V (factor V Leiden), and prothrombin (prothrombin 20210A) have been clearly implicated in venous thrombosis; however, their association with arterial strokes in adults is less clear. Their importance is probably greatest in the context of venous thrombosis with paradoxical embolism and cerebral venous sinus thrombosis. Tests for these abnormalities are best applied selectively. 

IV. LARGE VESSEL DISEASE

ANTERIOR CIRCULATION

The common carotid arteries arise from the aortic arch (via the innominate artery on the right). The bifurcation of the common carotid artery yields the ICA and ECA. The ICA travels in the neck (cervical segment) to enter the carotid canal at the base of the skull. It then travels through the petrous bone (petrous segment), enters the cavernous sinus (cavernous carotid, carotid siphon), and finally emerges into the subarachnoid space adjacent to the pituitary stalk (supraclinoid segment). Entering the circle of Willis, the ICA gives off the ophthalmic artery, the posterior communicating artery, and the anterior choroidal artery before it bifurcates to form the ACA and MCA.

Atherosclerosis commonly affects the origin of the ICA. Stenosis, occlusion, and distal embolization may cause any of the stroke syndromes seen with cardioembolic occlusion of the MCA and ACA as well as their branches. Yet patients with severe disease may be asymptomatic. The manifestations of this lesion depend largely on the pattern of collateralization and on the activity of the atherosclerotic plaque. Recent TIAs in the ICA field, including transient monocular blindness, may precede completed strokes. When a stenotic lesion is severely flow limiting, the history may show that the patient wakes up with a new deficit. Atherosclerosis may also affect the intracranial ICAs, often in the cavernous segment. Intracranial stenosis may affect the proximal MCAs and other vessels. This stenosis is most commonly seen in patients with severe atherosclerotic risk factors (including diabetes mellitus) and with accelerated disease; it is more common in blacks and Asians than in Caucasians. Recurrent TIAs in the same territory suggest a fixed lesion that is limiting flow or providing a source for artery-to-artery emboli. Atherosclerosis of the ascending aorta and arch has been recognized as an important source of cerebral emboli.

POSTERIOR CIRCULATION

The vertebral arteries (VA) arise from the subclavian arteries and ascend in the neck within the transverse foramina of the cervical vertebrae. Before converging to form the BA, each VA gives off a PICA. The PICA supplies the posterior cerebellum and, sometimes, the lateral medulla. In most cases, the lateral medulla is supplied not by the PICA but by small penetrating arteries arising from the distal VA. The anterior inferior cerebellar arteries and the SCA (which are circumferential branches of the BA) supply the middle cerebellar peduncle and cerebellum. Along its length, the BA gives off penetrating arteries that supply the pons and midbrain. The BA terminates in the bifurcation forming the 2 PCAs.

Occlusion of the VA (usually at its origin by atherosclerotic plaque or at C2 by dissection) may cause lateral medullary infarction (Wallenberg’s syndrome). This syndrome is characterized by (1) ipsilateral ataxia (inferior cerebellar peduncle or cerebellum); (2) nystagmus (which is usually horizontal and rotatory) that is accentuated by gaze to the ipsilateral side (vestibular nuclei); (3) contralateral hypertrophic skew deviation whereby the contralateral eye is higher (vestibular nuclei); (4) ipsilateral ptosis and miosis; (5) Horner’s syndrome (ascending sympathetic fibers); ipsilateral facial sensory loss and loss of corneal reflex (nucleus and tract of V); contralateral pain and temperature loss on the body (spinothalamic tract); and ipsilateral palatal weakness and hoarseness (nucleus ambiguous). The cerebellum is usually spared because of collateral flow, but it may be involved in some cases. Unilateral VA occlusion is often tolerated without symptoms, especially because distal flow to the BA has a dual supply.

BA stenosis may cause TIAs localizing to the pons or may cause devastating pontine infarction with pinpoint...
pupils, horizontal gaze paresis, internuclear ophthalmoplegia, and central nystagmus; facial sensory loss and weakness; hearing loss; vertigo; dysarthria; dysphagia; quadriplegia; and respiratory failure. Maintenance of consciousness depends on the perfusion of the ascending RAS in the upper pons and midbrain. When the BA is occluded, consciousness may be the only spared function along with vertical eye movements causing the “locked-in syndrome” in patients with filling of the basilar tip via the posterior communicating artery collaterals. A BA atheroma may occlude the ostium of a penetrating vessel to cause a discrete lacunar stroke mimicking small vessel disease. Patients with transient ischemia caused by flow-limiting stenosis of the BA may have transient symptoms. Although recurrent isolated vertigo is rarely the only indication of major basilar stenosis, it can be the first symptom; therefore, care must be taken in evaluating such patients, especially those with vascular risk factors.

**PATHOPHYSIOLOGIC MECHANISMS OF LARGE VESSEL DISEASE**

The 2 major mechanisms of infarction caused by large vessel disease are (1) limitation of distal blood flow by a severely stenotic or occluded vessel, and (2) artery-to-artery embolism. The recurrence of events in a single vessel territory suggests that a fixed vascular stenosis can result from either of these mechanisms.

Border-zone, or watershed, infarction suggests a flow-limiting lesion. ACA-MCA border-zone ischemia causes a paramedian strip of frontal and parietal infarction, which affects the leg and the proximal upper extremity causing the typical “man-in-a-barrel” pattern of weakness. PCA-MCA border-zone ischemia causes infarction in the dorsal accessory visual cortex causing Balint’s syndrome, which is characterized by (1) optic ataxia; (2) ocular apraxia; and (3) simultanagnosia. A deep hemispheric watershed also occurs at the extremities of the lenticulostriate and cortical penetrating vessels. Ischemia by this mechanism may cause a slowly progressive stroke.

Artery-to-artery embolism is usually caused by platelet-fibrin thrombi. However, cholesterol embolism from an active atheromatous plaque may also occur. This embolism is commonly seen after instrumentation (eg, cardiac catheterization) in patients with ascending aortic atheroma. Occasionally, patients with large active atheroma will embolize large amounts of cholesterol crystals causing a systemic crystalline vasculitis with multifocal cerebral ischemia, acute renal failure, embolic skin lesions, fever, and increased ESR.

The most common underlying large vessel lesion is the atheromatous plaque; however, arterial dissection is also common and increasingly recognized because of adequate imaging. In young patients, arterial dissection competes with cardioembolism as the most common cause of stroke. Dissection of the carotid or vertebral arteries is most common. This lesion can also cause symptoms either by distal embolization of thrombus formed at the site of the endothelial tear or by limitation of flow because of large vessel stenosis when the true lumen is compressed by hematoma in the false lumen. Dissections may be spontaneous or caused by trauma. Fibromuscular dysplasia, type IV Ehlers-Danlos syndrome, and Marfan’s syndrome should be considered although in most cases no underlying vasculopathy is found. Other large vessel vasculopathies are rare (Table 1).

**D I A G N O S I S OF I S C H E M I C S T R O K E**

**Table 1**

<table>
<thead>
<tr>
<th>Diagnosis of Ischemic Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Large Vessel Stroke</strong></td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
</tr>
<tr>
<td><strong>CT Imaging</strong></td>
</tr>
<tr>
<td><strong>MRI</strong></td>
</tr>
</tbody>
</table>

Evaluation begins with syndrome identification. CT and MRI may show single or multiple cortical-based, wedge-shaped lesions typical of embolism or may show a distribution of gray and white matter infarction in a vascular watershed. Time-of-flight MRA and CT angiography allow noninvasive visualization of blood flow (MRI) and vessel caliber (CT angiography). Gadolinium-enhanced MRA now allows dye contrast imaging of the vessels with the MR technique. Although these techniques are not yet sensitive or specific enough to replace conventional angiography in all cases, they allow adequate noninvasive diagnosis in most cases.

Time-of-flight MRI visualizes blood flow. Interpretation must carefully account for artifacts caused by direction of flow and by turbulent flow in tortuous vessels. It must be kept in mind that this technique tends to overestimate the degree of stenosis in the setting of very reduced flow. However, complete dropout of the signal column suggests significant stenosis. MRA with gadolinium enhancement may offer improved specificity. CT angiography has the advantage of being a true contrast image; in addition, it can be done rapidly and can quickly assess patients with acute stroke for whom a very rapid study is needed for treatment planning. As technology develops, better visualization of a larger number of distal vessels is being achieved. Both MR and CT techniques provide the advantage of multiplanar visualization.

In patients with arterial dissection, blood in the subacute phase within the false lumen can often be seen on T1-weighted and T2-weighted images as a crescent of bright signal within the vessel wall. The fat-suppression technique increases the specificity of MRI for diagnosis of dissection. This technique now allows routine noninvasive diagnosis of dissection.

Carotid ultrasound with gray scale and color flow imaging is most useful to evaluate the carotid arteries.
because, in many cases, it allows for accurate estimation of the degree of stenosis, characterization of the atherosclerotic plaque features, and detection of dissection. Transcranial Doppler ultrasound can supplement carotid ultrasound to answer specific questions about intracranial flow.

V. SMALL VESSEL DISEASE

Small penetrating vessels supply the white matter and deep gray structures throughout the brain. Occlusion of these small vessels typically causes syndromes characterized by a lack of classical cortical features (eg, aphasia, agnosia, apraxia, neglect, cortical sensory loss) and by presence of dysarthria, intact visual fields, and often isolation of the sensory or motor system with an extensive deficit encompassing the full hemibody. These features occur because of the deep localization of such infarctions where they fail to involve the cerebral cortex and where they may affect motor fibers collected compactly into projection tracts or sensory nuclei in the thalamus. The basis pontis, cerebellum, internal capsular, basal ganglia, thalamus, and deep hemispheric white matter are the most common sites for these small, deep infarctions. Classic features are described in the following sections.\textsuperscript{38}

**Table 1. Some Uncommon Causes of Stroke**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Specific Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon embolic material</td>
<td>Endocarditis, air embolism, fat embolism, amniotic fluid embolism, tumor (eg, left atrial myxoma), vascular catheters and devices</td>
</tr>
<tr>
<td>Uncommon large vessel diseases</td>
<td>Accelerated atherosclerosis (eg, homocystinemia, postradiation therapy), fibromuscular dysplasia and intimal dysplasia, moyamoya, large vessel vasculitis (eg, temporal arteritis, Takayasu’s syndrome, periar teritis nodosa, Churg-Strauss angiitis), infectious vasculitis (eg, herpes zoster, aspergillosis, mucormycosis, etc)</td>
</tr>
<tr>
<td>Uncommon small vessel diseases</td>
<td>Small vessel vasculitis (eg, hypersensitivity vasculitis), infections (eg, syphilis, tuberculosis, fungi)</td>
</tr>
<tr>
<td>Cerebral venous sinus thrombosis with venous infarction</td>
<td></td>
</tr>
<tr>
<td>Prothrombic states (see text)</td>
<td>Oral contraceptive use, pregnancy, and puerperium; APAS; sickle cell disease; cancer; myeloproliferative disorders; DIC; TTP; HIT; inherited and acquired protein deficiencies (protein C, S, ATIII); other inherited clotting disorders (Leiden V, prothrombin 20210A mutations) (see text)</td>
</tr>
<tr>
<td>Other inherited disorders of metabolism and structure</td>
<td>CADASIL, MELAS, Fabry’s disease, homocystinuria, fibromuscular and intimal dysplasia, Marfan’s syndrome, Ehlers-Danlos syndrome type IV</td>
</tr>
</tbody>
</table>

APAS = antiphospholipid antibody syndrome; ATIII = antithrombin III; CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarctions and leukoencephalopathy; DIC = disseminated intravascular coagulation; HIT = heparin-induced thrombocytopenia; MELAS = mitochondrial encephalopathy with lactic acidosis and stroke-like episodes; TTP = thrombotic thrombocytopenic purpura.

**PURE MOTOR STROKE**

This stroke causes weakness on one side of the body, which usually involves the face, arm, and leg more or less equally; patients do not have visual field defects, sensory signs, or dysarthria nor do they have aphasia, neglect, or other cortical signs. In some patients with pontine lesions, the face will be spared. It is common for patients to present with weakness that is limited in degree or extent. The full syndrome will develop over several days in some patients. Most patients with this syndrome have a small infarction in the contralateral internal capsule, basis pontis, or corona radiata.

**PURE SENSORY STROKE**

Patients may develop sudden sensory loss on one side of the body without other symptoms or signs. As with pure motor stroke, the complete hemibody is often involved; on examination, a deficit is often found on the torso and on the extremities. As with pure motor stroke, partial syndromes may also occur. Most patients with pure sensory stroke have a small infarction in the contralateral thalamus.

**DYSARTHRIA–CLUMSY HAND SYNDROME AND ATAXIC HEMIPARESIS**

Isolated dysarthria and arm or leg weakness may occur
because of small deep infarctions, usually in the pons where motor fibers are separated. Ataxia with full hemiparesis may occur because of a lesion in the basis pontis or in the internal capsule, the latter probably affecting cerebellar projection fibers to the ventral anterior–ventral lateral thalamus.

**SENSORIMOTOR STROKE**

Extensive sensory and motor deficits without visual field defects or cortical signs may also occur. These deficits are usually caused by a large deep stroke in the striatocapsular area or corona radiata. As the location of deep hemispheric infarction moves rostrally into the fan of the corona radiata, less extensive deficits are more likely to occur.

In addition to these classic lacunar syndromes, several uncommon named syndromes with localizing value may be caused by lesions in the brainstem. These brainstem syndromes are characterized by ipsilateral facial deficits (due to involvement of cranial nerve nuclei and intramedullary cranial nerve fascicles) and by contralateral deficits of the body (due to involvement of crossed long tracts, especially the corticospinal tract). Some of these named syndromes are described in Table 2.

Small cerebral arterioles undergo chronic changes, termed lipohyalinosis because of chronic hypertension and atherosclerosis. Accumulation of such changes can cause the lumen of these vessels to narrow and ultimately occlude, resulting in small deep infarctions (lacunar infarctions). As previously noted, whenever the clinical syndrome suggests a small vessel pathology, the parent large vessel should be evaluated because occlusion at the ostium of a small vessel may be caused by large vessel disease (Figure 2). Embolism and small hemorrhages may also mimic lacunar strokes. Therefore, although the identification of these syndromes has some value in predicting underlying pathophysiology, it is always important to keep large vessel disease, embolism, and hemorrhage in mind when assessing patients with these syndromes.

**VI. UNCOMMON STROKE DIAGNOSES**

Most strokes are caused by embolism, large vessel disease, or small vessel disease, which are attributable to underlying cardiac disease, atherosclerosis, hypertension, and dissection; however, physicians should be aware of uncommon stroke mechanisms as well as the causes and clinical situations in which they arise. During arterial instrumentation, embolization of air or parts from vascular catheters and devices may occur. In addition, fat may embolize after long bone fracture, or amniotic fluid may embolize during labor. Embolization of tumor fragments or thrombi may occur with left atrial myxoma. This tumor has many systemic manifestations and may mimic endocarditis or vasculitis. Patients with myxoma often have fever, weight loss, arthralgias, and increased ESR. Cerebral vasculitis may be a manifestation of a systemic vasculitic syndrome, or it may occur in isolation, in which case the presentation is nonspecific: evidence of focal, multifocal, or diffuse encephalopathy usually with a subacute temporal profile and small deep infarctions on CT or MRI scanning. Some of these infarctions may enhance slightly. Diagnosis may be suggested by cerebral angiograms

---

**Table 2. Uncommon Midbrain and Pontine Syndromes**

<table>
<thead>
<tr>
<th>Eponym</th>
<th>Location</th>
<th>Clinical Deficits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Millard-Gubler</td>
<td>Caudal basis pontis</td>
<td>Contralateral hemiplegia</td>
</tr>
<tr>
<td></td>
<td>Fascicles of CN V1 and VII</td>
<td>Ipsilateral abducens and facial palsy</td>
</tr>
<tr>
<td>Foville</td>
<td>Caudal basis pontis</td>
<td>Contralateral hemiplegia</td>
</tr>
<tr>
<td></td>
<td>Nucleus/fascicle of CN VII</td>
<td>Ipsilateral facial palsy</td>
</tr>
<tr>
<td></td>
<td>Paramedian pontine reticular formation</td>
<td>Ipsilateral gaze paresis (“wrong way eyes”)</td>
</tr>
<tr>
<td>Weber</td>
<td>Cerebral peduncle</td>
<td>Contralateral hemiplegia</td>
</tr>
<tr>
<td></td>
<td>Fascicle of CN III</td>
<td>Ipsilateral oculomotor palsy</td>
</tr>
<tr>
<td>Benedikt</td>
<td>Red nucleus, superior cerebellar peduncle</td>
<td>Contralateral tremor or chorea</td>
</tr>
<tr>
<td></td>
<td>Fascicle of CN III</td>
<td>Ipsilateral oculomotor palsy</td>
</tr>
<tr>
<td>Claude</td>
<td>Superior cerebellar peduncle</td>
<td>Contralateral cerebellar ataxia</td>
</tr>
<tr>
<td></td>
<td>Fascicle of CN III</td>
<td>Ipsilateral oculomotor palsy</td>
</tr>
</tbody>
</table>

CN = cranial nerve.
showing segmental arterial narrowing; however, this finding is also nonspecific. If associated clinical features of systemic vasculitis do not provide a convincing explanation, brain biopsy is usually needed to distinguish vasculitis from diseases such as intravascular lymphoma, which mimic vasculitis in their presentation. The possibility of cerebral venous sinus thrombosis with infarction is suggested by bilateral deficits, seizures, parasagittal or temporal infarctions not conforming to arterial territories and often with a hemorrhagic component, and hypercoagulable states (eg, late pregnancy, puerperium).

Thrombocytopenia should prompt a search for various hematologic disorders that may cause stroke, such as disseminated intravascular coagulation; thrombotic thrombocytopenic purpura (TTP); severe toxemia of pregnancy with microangiopathic hemolytic anemia, elevated liver enzymes, and low platelet count (HELLP syndrome); heparin-induced thrombocytopenia; and the antiphospholipid antibody syndrome. A family history of vascular disease should raise suspicion for one of the uncommon familial disorders that may cause stroke. Many of these are associated with phenotypic clues. Genetic testing is now available for mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS) and for cerebral autosomal dominant arteriopathy with subcortical infarctions and leukoencephalopathy (CADASIL). Table 1 lists many uncommon causes of stroke.

**VII. CASE PRESENTATIONS**

**CASE PATIENT 1**

Patient 1 is a 68-year-old man with chronic hypertension who states he has had sudden onset of right arm and leg weakness. In the emergency department, he is found to have severe weakness of the right lower face as well as the right arm and leg. He is alert and oriented. Speech and language are normal. The visual fields are full. Sensation is normal. He has a right Babinski’s sign.

- **This deficit is likely to be caused by which of the following lesions? Choose all that apply.**
  A) Left VA occlusion
  B) Left MCA stem embolism
  C) Top of the basilar embolism
  D) Left internal capsule lacunar infarction

**Figure 2.** Large vessel disease mimicking small vessel (lacunar) disease. CT angiogram of a 61-year-old man with hypertension and coronary heart disease who presented with severe dysarthria and left hemiparesis with no aphasia or sensory deficit. All symptoms resolved over several hours. MRI showed an acute infarction in the right basis pontis consistent with occlusion of a paramedian pontine penetrating artery. This frontal plane CT angiogram shows that this lesion is likely caused by severe atheromatous disease in the midbasilar artery. The white arrow shows the site of stenosis. Calcium can be seen in the vessel wall. CT = computed tomography; MRI = magnetic resonance imaging.
The correct answers are B and D. The sudden onset of pure motor hemiplegia involving the face, arm, and leg that spares cortical function (in this instance, language is spared); spares visual fields; and spares sensory function is characteristic of a pure motor stroke. This type of stroke often results from a lenticulostriate small vessel occlusion causing a lacunar infarction in the internal capsule. This stroke could also be caused by a lacunar stroke in the pons. In some cases, dysarthria and hemiataxia will accompany the hemiparesis with such lesions. However, an MCA stem embolism in the setting of good cortical collateralization may also be possible. A lesion sparing the MCA cortical fields can clinically mimic the pure motor lacunar stroke. A stroke could also occur in the less common setting of intracranial atherosclerotic plaque involving the MCA stem and occluding the ostium of a penetrating lenticulostriate vessel. The integrity of the feeding vessel should be considered in all cases that clinically suggest small vessel disease.

CASE PATIENT 2

Patient 2 is a 55-year-old man with chronic atrial fibrillation. He is brought to the emergency department by his wife because he has been confused during the course of the day. Head MRI shows evidence of acute infarction in the posterior inferior hemispheres in the areas of the temporo-occipital junctions that is bilaterally consistent with embolic stroke in the territory of both posterior cerebral arteries. The primary visual cortex is spared.

- This lesion is likely to cause all of the following deficits EXCEPT:
  A) Prosopagnosia
  B) Color agnosia
  C) Optic ataxia
  D) Achromatopsia

The correct answer is C. Ventral lesions in the visual association cortex in the temporo-occipital region typically cause visual agnosias. These agnosias may include prosopagnosia (inability to recognize faces), color agnosia (inability to name colors), and achromatopsia (inability to sort by color). On the other hand, optic ataxia, the inability to perform localizing movements in space, is a feature of Balint’s syndrome (optic ataxia, ocular apraxia, and simultanagnosia). Balint’s syndrome is caused by dorsal posterior lesions in the region of the parieto-occipital junction. A mnemonic for this is that the ventral visual association cortex tells one WHAT things are, whereas the dorsal visual association cortex tells one WHERE things are.

CASE PATIENT 3

Patient 3 is a 69-year-old man who states he has had sudden onset of left frontal headache, double vision, and dizziness. On examination, he is noted to have a right hypertropic skew deviation, left-beating nystagmus, and left-sided miosis and ptosis. His voice is hoarse, and his palate does not elevate well on the left side.

- Other deficits that are likely to be found include all of the following EXCEPT:
  A) Loss of left corneal reflex
  B) Left-sided appendicular ataxia
  C) Right-sided loss of pain and temperature on the body
  D) Left-sided tongue deviation

The correct answer is D. The lateral medullary syndrome (Wallenberg’s syndrome) is usually caused by occlusion of the VA resulting in decreased flow in the penetrating arteries to the lateral medulla arising from the distal VA in most cases. The full syndrome includes ipsilateral cerebellar ataxia; nystagmus (which is usually horizontal and rotatory) that is accentuated with ipsilateral gaze; contralateral hypertropic skew; ipsilateral Horner’s syndrome; ipsilateral facial sensory deficit including loss of the corneal reflex; contralateral loss of temperature and pain sensation on the body; and ipsilateral palatal weakness and diaphragmatic paralysis causing hoarseness. The hypoglossal nucleus and nerve subserving motor function of the tongue are located medially in the medulla.

CASE PATIENT 4

Patient 4 is a 71-year-old man with a history of chronic hypertension who presents with horizontal diplopia greatest on leftward gaze, weakness involving the left upper and lower face, right hemiplegia, and Babinski’s sign.

- The lesion is likely to be in which of the following?
  A) Left rostral basis pontis
  B) Left cerebral peduncle
  C) Left caudal basis pontis
  D) Left lateral medulla

The correct answer is C. Brainstem lesions typically cause crossed face and body deficits. Patient 4 has the Millard-Gubler syndrome characterized by left abducens palsy, a left peripheral facial nerve palsy, and a left corticospinal tract lesion above its decussation at the spino-medullary junction (Table 2). The abducens nucleus and the intramedullary portion of the abducens nerve are
located in the caudal pontine tegmentum near the midline and just below the fourth ventricle. The facial nucleus is located more laterally, and its intramedullary nerve fibers loop around the abducens nucleus before emerging laterally from the caudal pons. Thus, a lacunar infarction in the caudal basis pontis can injure corticospinal tract fibers in this area as well as the intramedullary portions of the abducens and facial nerves. With Millard-Gubler and other brainstem lesions, it is the deficits caused by nuclear and intramedullary nerve fibers (and not the long tract signs) that allow the localization of the lesion along the longitudinal axis of the brainstem. The best known example of this principle is Wallenberg’s syndrome in which the nucleus ambiguous lesion causes palatal weakness and hoarseness that clearly establish the lateral medullary localization.

**CASE PATIENT 5**

Patient 5 is a 34-year-old woman who is brought to the emergency department by her husband who reports that she developed sudden onset of drowsiness and weakness several hours earlier. She is gravida 2, para 1 and has a history of one miscarriage at 14 weeks. Her last menstrual period was 2 weeks ago. There is no history of stroke, TIA, or thrombosis. She does not abuse drugs or alcohol. Her temperature is 98.8°F. Her pulse is 84 bpm and regular. Her blood pressure is 138/86 mm Hg. Livedo reticularis is observed on her back, abdomen, and thighs. She has a soft systolic murmur at the base and apex. The carotid pulses are normal with no bruit.

She must be repeatedly stimulated to maintain arousal. There is no blink to threat from the right. There is bilateral ptosis. The pupils are asymmetric: the left is 5 mm and sluggishly reactive, whereas the right is 4 mm and slightly ovoid. She cannot be coaxed to look upward. With a penlight reflection on the corneas, the left eye appears to be slightly higher than the right. She moves the left side slightly more spontaneously than the right. Laboratory data include: leukocyte count, 9000 cells/mm³; hematocrit, 34%; platelets, 110,000/mm³; smear, mild hypochromia and microcytosis; blood urea nitrogen, 24 mg/dL; creatinine, 0.8 mg/dL; INR, 1.1; PTT, 28 seconds; and fibrinogen, 390 mg/dL. A urine pregnancy test is negative.

- **Patient 5 has most likely had infarction in which of the following structures?**
  A) Left basal ganglia and internal capsule  
  B) Midbrain tegmentum  
  C) Caudal pontine tegmentum  
  D) Left hemisphere and insular cortex

- **The most likely mechanism and vascular lesion is in which of the following?**
  A) BA thrombosis  
  B) VA dissection  
  C) Basilar tip embolism  
  D) Lacunar stroke of the midbrain

- **The most likely cause of patient 5’s infarction is which of the following?**
  A) Thrombotic thrombocytopenic purpura  
  B) HELLP syndrome  
  C) Antiphospholipid antibody syndrome  
  D) Disseminated intravascular coagulation

The correct answers are B, C, and C, respectively. Patient 5’s disconjugate gaze places the lesion in the infratentorial region eliminating further consideration of choices A and D, at least as the lone sites of infarction. An impaired level of consciousness is caused by involvement of the midbrain ascending RAS, ptosis is caused by involvement of the oculomotor subnucleus for the levator palpebrae, and impaired upgaze is caused by involvement of upper midbrain centers for gaze integration. Pupils that are large to midrange, unequal, irregular, and poorly responsive to light are characteristic of midbrain lesions. Large pontine lesions may affect the ascending RAS in the upper pons, but these lesions typically cause pinpoint pupils. Pontine lesions impair horizontal gaze sparing vertical gaze. Lesions limited to the caudal pons are below the ascending RAS and do not impair consciousness.

Although any of these vascular lesions could have occurred, a young woman without early accelerated atherosclerosis is most likely to have embolism either from the heart or from dissection as the cause of her lesion. Case 5 is the typical presentation of a patient with top of the basilar embolism. Although this type of infarction could result from VA dissection, other features of the case suggest cardiac source embolism.

Although all of these disorders should be considered in a patient with stroke and thrombocytopenia, patient 5 has the major features of the antiphospholipid antibody syndrome: thrombotic event, second trimester abortion, and thrombocytopenia. Livedo reticularis is also a common finding in this disorder. Lack of fever, microangiopathic hemolytic anemia, or renal involvement argue against TTP. Also, when neurologic events occur in TTP, the platelet count is usually much lower. Disseminated intravascular coagulation would be expected to cause fibrinogen consumption and elevation of INR and PTT because of clotting factor consumption. The isolated mild elevation of the PTT is the most common laboratory
abnormality found in the screening coagulation tests in antiphospholipid antibody syndrome, although it is usually not present.

HELLP syndrome must occur in the context of late pregnancy or the puerperium. Also, it should cause microangiopathic hemolytic anemia.

VIII. SUMMARY POINTS

• The operational definition of acute ischemic stroke is the sudden onset of an acute focal neurologic deficit, which should initiate a diagnostic evaluation.
• The clinical diagnosis of stroke begins with an application of classical neurologic principles of topographic localization, which are based on a solid foundation of functional neuroanatomy.
• Neurologic localization based on the examination should be followed by an attempt to localize the site of the vascular stenosis or occlusion.
• Knowledge of classical stroke syndromes can aid in the clinical diagnosis. However, care must be taken to avoid misdiagnosis based on narrow interpretation of the possible lesions that may underlie a particular clinical pattern. For example, embolism is a major mechanism of stroke in large vessel disease, and large vessel disease leading to occlusion of the ostium of a penetrating vessel may mimic small vessel occlusion because of lipohyalinosis.
• To establish the site and size of infarction as well as the site and nature of the vascular lesion, diagnosis should be supplemented by CT or MRI scanning with vascular imaging when available.
• With the knowledge of the site of the infarction and the nature of the vascular lesion, a laboratory evaluation should be planned to establish the pathophysiologic mechanisms that underlie the stroke so that rational acute and preventive therapies can be implemented.
• Although stroke is common, uncommon causes of stroke should be ruled out in atypical cases.

REFERENCES


