

Ischemic Stroke: Pathophysiology and Principles of Localization

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

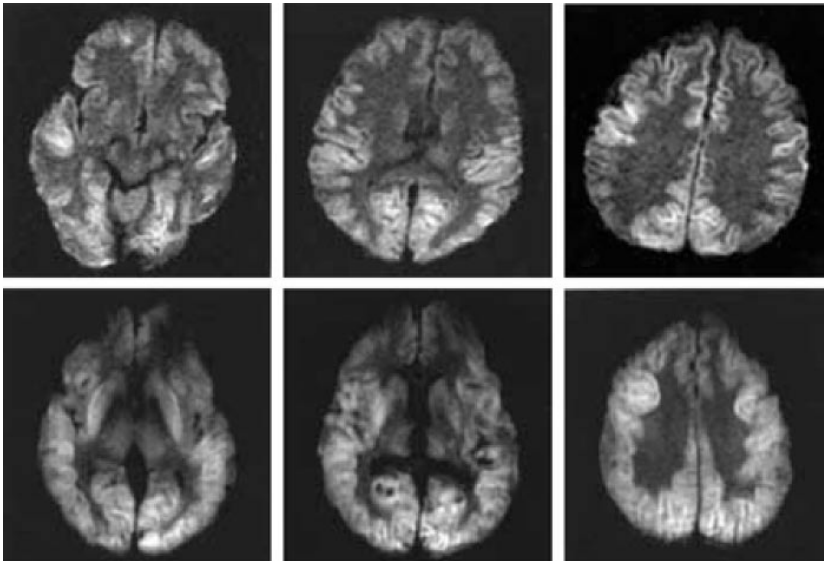


Figure. Magnetic resonance image obtained in evaluation of patient in question 2. (Reprinted with permission from Barrett KM, Freeman WD, Weindling SM, et al. Brain injury after cardiopulmonary arrest and its assessment with diffusion-weighted magnetic resonance imaging. *Mayo Clin Proc* 2007;82: 828–35.)

QUESTIONS

1. Vasospasm and ischemic stroke are frequent complications of aneurysmal subarachnoid hemorrhage (SAH). Nimodipine, a calcium channel antagonist, has been shown to improve outcomes when administered soon after diagnosis of SAH. What is the most likely mechanism?

- (A) Prevention of segmental arterial vasospasm by relaxing arterial smooth muscle
- (B) Reduced severity of SAH-associated myocardial shock by diminishing cardiac afterload
- (C) Reduction of pathologic calcium influx in ischemic cells, inhibiting apoptosis
- (D) Vasodilation of the cerebral vasculature facilitating passive perfusion

2. A 28-year-old woman is found on the floor by a friend. The patient is a known intravenous heroin user. On arrival to the hospital, the patient is obtunded. She receives several doses of naloxone, but her mental status fails to improve. On examination, she is unresponsive except for decorticate posturing in response to noxious stimulation. Brainstem reflexes are intact. Diffusion-weighted magnetic resonance imaging (MRI) is performed 1 week later (**Figure**). What is the most likely mechanism of this patient's neurologic impairment?

- (A) Acute spongiform encephalopathy from heroin inhalation ("chasing the dragon")
- (B) Bacterial meningitis
- (C) Bilateral middle cerebral artery infarctions
- (D) Bilateral watershed infarctions
- (E) Hypoxia

Dr. Maas is a fellow in Stroke and Neurocritical Care, Harvard Medical School, Departments of Neurology, Massachusetts General and Brigham and Women's Hospitals, Boston, MA. Dr. Safdieh is an assistant professor of neurology, Department of Neurology and Neuroscience, Weill Medical College of Cornell University, New York, NY.

3. A 64-year-old man collapses in a public place. Emergency medical service (EMS) personnel arrive after approximately 7 minutes, begin cardiopulmonary resuscitation, and apply a defibrillator successfully to treat ventricular fibrillation. Due to the quick EMS response and excellent inpatient care for his cardiac disease, the patient achieves a good recovery. If the patient were to be examined 6 months after the event, what neurologic deficit attributable to the cardiac arrest is most likely to be encountered?

- (A) Ataxia
- (B) Lower extremity spasticity (spastic diplegia)
- (C) Peripheral large fiber sensory neuropathy
- (D) Short-term memory impairment

Questions 4 and 5 refer to the following case.

4. A 38-year-old man presents to the emergency department complaining of an episode of left arm heaviness and clumsiness that lasted for approximately 5 minutes. The patient is no longer concerned about the event. However, he explains that he has not felt well for the past 2 days and stayed awake with chills the night before. He is sure the event was caused by being tired. The neurologic examination is normal. The general examination is notable for a mild heart murmur, which the patient states has been present since childhood, and some scarring on the forearms and antecubital areas. The patient reports no family history of neurologic disease. Based on the information presented, which mechanism of cerebral ischemia appears to be most plausible?

- (A) Cardioembolism
- (B) Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
- (C) Cerebral vasculitis
- (D) Lipohyalinosis
- (E) Mitochondrial encephalomyopathy lactic acidosis and stroke-like episodes (MELAS)

5. The patient is diagnosed with infectious endocarditis, and an appropriate antibiotic regimen is started. The next day, he reports that he is experiencing some abnormal difficulty reading the newspaper, which had not been a problem for him 5 minutes prior when he set the paper down to use the bathroom. A second evaluation reveals that he has no problem speaking or understanding speech or writing, but he is unable to read. He also has a right homonymous hemianopia. What is the likely location of his lesion?

- (A) Left anterior choroidal territory
- (B) Left inferolateral frontal lobe
- (C) Left occipital lobe extending to the splenium of the corpus callosum
- (D) Left superior temporal lobe

Questions 6–9 refer to the following case.

A 45-year-old woman presents to the emergency department complaining of sudden vision loss in her right eye. She was recently diagnosed with hypertension and takes hydrochlorothiazide. She reports no other active medical problems and has no history suggestive of transient ischemic attack or stroke. Her concerned friend reports that the patient has been struggling at work lately. Her coworkers have complained that she is uncharacteristically rude and abrupt, and her job performance has been erratic. The last audit she performed in her capacity as an accountant contained several errors. The patient has begun seeing a therapist and has blamed her recent problems on feeling depressed.

6. Several cerebrovascular disease syndromes include cognitive and psychiatric findings. Which of the following conditions does not have cognitive dysfunction as a prominent characteristic?

- (A) Behçet's disease
- (B) CADASIL
- (C) Fibromuscular dysplasia
- (D) Lupus cerebritis
- (E) Primary angiitis of the central nervous system (CNS)

7. Evaluation by an ophthalmologist reveals a branch retinal artery occlusion. On mental status examination, she shows mild memory impairment and is unable to perform serial 7s. Neurologic examination is significant for decreased hearing bilaterally. She has no family history of similar neurologic problems and no abnormal skin findings. Which of the following diagnoses is most consistent with this patient's clinical presentation?

- (A) CADASIL
- (B) Giant cell arteritis
- (C) MELAS
- (D) Sneddon's syndrome
- (E) Susac's syndrome

8. An MRI of the brain is obtained to provide confirmatory evidence for this patient's condition. Which of the following findings is most consistent with Susac's syndrome?

- (A) Diffuse white matter hyperintensity on fluid attenuation inversion recovery (FLAIR) images sparing the subcortical U fibers
- (B) Hyperintensity on FLAIR images in the central portion of the corpus callosum
- (C) Punctate areas of hypointensity on gradient echocardiography images
- (D) Sulcal hyperintensity on T2 images
- (E) White matter hyperintensity on FLAIR images predominantly in the occipital lobes

9. Research on Susac's syndrome indicates a pathologic role of antiendothelial cell antibodies. Several autoimmune conditions can lead to cerebral infarction. A pathologic self-recognizing antibody has been identified for which of the following presumably autoimmune stroke-causing conditions?

- (A) Behçet's disease
- (B) Giant cell arteritis
- (C) Primary angiitis of the CNS
- (D) Sneddon's syndrome
- (E) Wegener's granulomatosis

ANSWERS

1. The correct answer is (C), reduction of pathologic calcium influx in ischemic cells, inhibiting apoptosis. Numerous trials have demonstrated the efficacy of nimodipine in treatment of SAH. Although nimodipine can reduce systemic vascular resistance (and thereby blood pressure) at higher doses and may also act on arterial smooth muscle in the cerebral vasculature, studies of nimodipine in SAH have shown no significant reduction in the incidence of symptomatic vasospasm or change in vessel caliber.¹ Nimodipine most likely acts to diminish the early pathologic calcium influx due to cellular ischemia, thereby functioning as a neuroprotectant that inhibits the apoptosis cascade.

Reference

1. Mayberg MR, Batjer HH, Dacey R, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage. A statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. *Stroke* 1994;25:2315–28.

2. The correct answer is (E), hypoxia. The diffusion-weighted images in the figure show an abnormal

hyperintensity of the cortex. All cortical surfaces are involved, and involvement is not limited to middle cerebral artery or watershed distributions. Although purulence from bacterial meningitis can cause hyperintensity on diffusion-weighted imaging, the signal change extends throughout the subarachnoid space including the sulci, whereas in these images the cortex itself is involved. Spongiform encephalopathy from heroin inhalation is a leukoencephalopathy with spongiform vacuolar degeneration of oligodendroglia, occasionally with pallidal damage.¹ The MRI finding shown in this figure is consistent with laminar necrosis, which is seen in conjunction with hypoxic ischemia injury. Many different pathologic processes can trigger hypoxic ischemia injury, including cardiac arrest, respiratory arrest, strangulation, near drowning, status epilepticus, and hypoglycemia. Respiratory arrest is a consequence of opiate intoxication, suggested by the patient's history of heroin use. The third layer of cortex (lamina III) is quite susceptible to ischemia, and grey matter is more vulnerable to ischemia than white matter. When blood flow is globally interrupted for a brief period, the cerebral white matter may survive the insult despite infarction of the cortex. Histologically, a band of necrosis can be seen in the middle layers of the cortex. This finding correlates to a poor prognosis for meaningful recovery.^{2,3}

In cases of severe hypoxic ischemia injury, cellular damage is widespread, while in milder cases damage may be subtle and limited. Not all neuronal populations are equally susceptible to ischemic damage. Brief episodes of global brain oxygen deprivation reveal an underlying pattern of vulnerability. Knowledge of the variable susceptibility is important for recognizing or predicting sequelae of events such as cardiac arrest. In question 3, the clinical consequences of hypoxic ischemia injury in a patient who survives such an event are considered.

References

1. Hill MD, Cooper PW, Perry JR. Chasing the dragon—neurological toxicity associated with inhalation of heroin vapour: case report. *CMAJ* 2000;162:236–8.
2. Barrett KM, Freeman WD, Weindling SM, et al. Brain injury after cardiopulmonary arrest and its assessment with diffusion-weighted magnetic resonance imaging. *Mayo Clin Proc* 2007;82:828–35.
3. McKinney AM, Teksam M, Felice R, et al. Diffusion-weighted imaging in the setting of diffuse cortical laminar necrosis and hypoxic-ischemic encephalopathy. *AJNR Am J Neuroradiol* 2004;25:1659–65.

- 3. The correct answer is (D), short-term memory impairment.** Several populations of neurons are particularly sensitive to ischemia, the most prominent of which are the CA1 layer of the hippocampus, basal ganglia, thalamus, Purkinje cells of the cerebellum, and layer III neurons of the cerebral cortex. Hippocampal damage appears to be the most likely, and most isolated complaints following cardiac arrest pertain to the memory domain. Careful examination may uncover subtle motor coordination deficits in many patients with isolated memory complaints, although overt ataxia or extrapyramidal findings are uncommon.¹

Reference

1. Lim C, Alexander MP, LaFleche G, et al. The neurological and cognitive sequelae of cardiac arrest. *Neurology* 2004;63:1774–8.

- 4. The correct answer is (A), cardioembolism.** With no family history of neurologic disease, CADASIL and MELAS are less probable. Furthermore, CADASIL and MELAS patients show prominent cognitive dysfunction. MELAS is a clinically diverse syndrome but usually presents at a much younger age and is accompanied by muscle fatigue, diabetes, and other signs. Many patients with vasculitis have systemic signs and symptoms, and the course is subacute with prominent encephalopathy. Lipohyalinosis is associated with older individuals with a history of diabetes and hypertension. This patient has signs of infection. Considering the scarring on his forearms and antecubital areas suggestive of intravenous drug use and the heart murmur, infectious endocarditis is of prominent concern. Up to 30% of patients with endocarditis develop neurologic symptoms.¹

Reference

1. Heiro M, Helenius H, Mäkilä S, et al. Infective endocarditis in a Finnish teaching hospital: a study on 326 episodes treated during 1980–2004. *Heart* 2006;92:1457–62.

- 5. The correct answer is (C), left occipital lobe extending to the splenium of the corpus callosum.** This patient has alexia without agraphia, a syndrome caused by a lesion of the left occipital lobe that extends to the splenium of the corpus callosum. The corpus callosum involvement prevents visual information from the right occipital lobe from reaching the receptive language areas in the left hemisphere. Infarcts of the left anterior choroidal

territory classically cause a triad of contralateral hemiparesis, hemisensory impairment, and visual field loss, although visual field loss is infrequent in most cases. Lesions in the left inferolateral frontal lobe, which involves Broca's area, cause prominent expressive aphasia. The left superior temporal lobe corresponds to Wernicke's area, and infarcts there manifest as receptive aphasia.

- 6. The correct answer is (C), fibromuscular dysplasia.** Behçet's disease, primary angiitis of the CNS, lupus cerebritis, and CADASIL all involve microvascular ischemia that may manifest as an encephalopathy with cognitive dysfunction, executive behavioral abnormalities, and psychiatric symptoms. Fibromuscular dysplasia is a large vessel vasculopathy, and diffuse cognitive and psychiatric symptoms are not characteristic.
- 7. The correct answer is (E), Susac's syndrome.** This patient's clinical presentation is most consistent with Susac's syndrome, a microvascular ischemic disease characterized by the clinical triad of encephalopathy, branch retinal artery occlusions, and hearing loss. A further description of the other diseases listed is provided in part I of this review.¹

Reference

1. Maas MB, Safdieh JE. Ischemic stroke: pathophysiology and principles of localization. *Hospital Physician Neurology Board Review Manual*. Volume 13, Part 1. February 2009.

- 8. The correct answer is (B), hyperintensity on FLAIR images in the central portion of the corpus callosum.** Virtually all patients with Susac's syndrome demonstrate involvement of the central white matter tracts of the corpus callosum on T2-weighted MRI images. Punctate hypointensities on gradient echocardiography images can be seen with amyloid angiopathy due to microhemorrhages. Sulci are always hyperintense on T2 images; the benefit of FLAIR sequences is suppression of cerebrospinal fluid (CSF) signal to allow for identification of lesions near CSF-containing spaces (ie, juxtacortical lesions). Occipital predominant FLAIR hyperintensity can be seen in a variety of other cerebrovascular diseases, such as posterior reversible encephalopathy syndrome. Diffuse leukoencephalopathy sparing the subcortical U fibers is the classic finding in metachromatic leukodystrophy.

9. The correct answer is (E), Wegener's granulomatosis. Wegener's granulomatosis is associated with cytoplasmic-staining antineutrophil cytoplasmic antibodies (c-ANCA). In the appropriate clinical context, a positive c-ANCA test and absent antinuclear antibodies is highly diagnostic. Behçet's disease, Sneddon's syndrome, giant cell arteritis, and primary angiitis of CNS are diagnosed by the presence

of the appropriate clinical features, with supporting evidence from nonspecific clinical tests such as erythrocyte sedimentation rate and biopsies.¹

Reference

1. Siva A. Vasculitis of the nervous system. *J Neurol* 2001; 248:451–68.

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