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Recognizing Stroke Mimics: A Guide for Primary Care

Background and Introduction

Acute ischemic stroke is a common and significant cause of mortality and morbidity in the United States, ranking fifth among all causes of death.[1,2] It affects upwards of 800,000 people per year.[3] Approximately 600,000 of these cases represent a first stroke, with the remainder representing recurrent strokes. Stroke also is a leading cause of permanent cognitive and function-limiting disability.[4,5] Therefore, given the significant associated mortality and morbidity, the American Heart Association's (AHA) Get with the Guidelines initiative emphasizes rapid recognition and potentially aggressive treatment of patients presenting with possible stroke symptoms.[6,7]

Prompt recognition of an acute ischemic stroke is crucial, since prior imaging-based work has demonstrated that the volume of irreversibly damaged brain tissue expands rapidly until reperfusion occurs.[8] In a recent U.S. registry study, rapid recognition followed by early thrombolytic treatment was associated with improved outcomes. For every 15-minute faster interval to treatment, stroke patients experienced reduced mortality and reduced symptomatic intracranial hemorrhage (sICH), as well as increased rates of independent ambulatory status at the time of discharge and discharge directly to home.[9]

However, timely recognition and treatment is complicated by the fact that there are multiple conditions that mimic acute ischemic stroke. A comprehensive review suggested that approximately 74% of patients presenting with apparent acute stroke symptoms ultimately were diagnosed with stroke, thus indicating that 26% of patients had their symptoms produced by "stroke mimics."[10] This estimation was similar to that from a 10-year study of more than 8,000 possible stroke patients evaluated by stroke teams, which found that 30% of patients had a stroke mimic.[11] More recent data reflect similar results, with one study focusing on telestroke cases reporting a stroke mimic rate of almost 25%, while another study of patients transferred from outlying hospitals with concern for acute ischemic stroke had a mimic rate of 17%, nearly all of whom received tissue plasminogen activator (tPA).[12,13] Therefore, prompt diagnosis is complicated by a multitude of stroke mimic etiologies, including structural intracranial abnormalities, infection, syncope, vertigo, seizure, and migraine patterns, as well as underlying psychiatric causes and demyelinating diseases.

Although the incidence of stroke mimics varies among the published studies, there are commonalities. Seizure, migraine, psychogenic disorders, and toxic/metabolic etiologies have been widely reported as among the most common nonvascular conditions that mimic stroke.[14-16] Data from a single hospital identified that common stroke mimics included seizures, syncope, sepsis, and functional disorders/conversion disorders.[17] (*See Table 1.*) Another center reported that toxic/metabolic disorders and seizure etiologies were most common.[14]

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EXECUTIVE SUMMARY

- Perform point-of-care glucose testing on patients with acute weakness or altered mental status.
- Many stroke mimics produce positive symptoms, whereas strokes predominately produce negative symptoms.
- Most strokes occur in patients with risk factors for cerebrovascular disease, whereas stroke mimics may or may not have such risk factors.
- Often, the diagnosis of a stroke mimic can be made only after an assessment has excluded an ischemic stroke.
- The risk of symptomatic intracranial hemorrhage when tissue plasminogen activator is given to a patient with a stroke mimic is about 1 in 200 — a rate at least three times lower than that seen in patients with acute ischemic stroke.

The wide array of potential stroke mimic etiologies often renders the clinical picture very difficult to distinguish from an acute ischemic process at the time of presentation. A factor that further complicates management is that patients may present within the appropriate thrombolysis administration window and subsequently receive this therapy. Although it has been suggested that up to 14% of mimic patients receive thrombolytics, it also has been postulated that there is decreased risk of associated adverse effects in this population.[14,15,18] There are no current data to suggest that tPA administration leads to adverse events in patients presenting with clinical features concerning for ischemic stroke but who ultimately are diagnosed with a stroke mimic.[19,20]

The key to avoiding unnecessary and potentially harmful therapy is improved understanding of the various mimic entities, as well as attention paid to important historical and physical exam features. In considering stroke symptoms, it can be helpful to think in terms of positive and negative symptoms. It has been explained elsewhere that positive symptoms are associated with excess central nervous system (CNS) activity and are characterized by visual disturbance, such as flashing lights and perception of various geometric shapes. In addition, somatosensory symptoms are associated with pain and/or paresthesias, and motor symptoms with jerking extremity movements. In contrast, negative symptoms are associated with a decrease in CNS function and commonly manifest as acute vision or hearing loss, as well as sensorimotor deficits in the extremities.[17] As a rule, acute ischemic stroke impairs CNS function manifested by negative symptoms. The three most common are unilateral subjective arm weakness, unilateral subjective leg weakness, and reported speech disturbance; positive symptoms are uncommon. Ischemia in the major cerebral vascular territories produces classic findings. (*See Table 2.*)

Although it may be difficult to rapidly differentiate such a wide array of etiologies from ischemic stroke, it has been suggested that several key features are associated with a potential stroke mimic profile, including younger patients, milder symptoms, arrival to the medical facility by means other than emergency medical services (EMS), and lack of cardiovascular risk factors.[11] Furthermore, several studies have suggested that patients with stroke mimics exhibit a lower prevalence of ischemic stroke risk factors.[15,19] One large, prospective study reported that specific historical factors associated with increased odds of having a stroke mimic included absence of hypertension, hyperlipidemia, and atrial fibrillation.[11] This is a dilemma that physicians will have to address continually as the treatment for acute stroke continues to evolve. The primary objective in this article is to review common stroke mimic etiologies, as well as discuss the key historical and physical examination characteristics associated with stroke mimics, and to present a diagnostic framework for approaching such cases.

Table 1. The Most Common Stroke Mimics

Seizure	20%
Syncope	15%
Sepsis	12%
Functional	9%
Primary headache disorder	9%
Brain tumor	7%
Metabolic	5%
Neuropathy	4%
Peripheral vestibular disorder	4%
Dementia	3%
Extra- or subdural hemorrhage	2%
Drugs and alcohol	2%
Transient global amnesia	2%
Other diagnoses	6%

Adapted from: Fernandes PM, Whiteley WN, Hart SR, et al. Strokes: Mimics and chameleons. *Pract Neurol* 2013;13:21-28.

Common Stroke Mimics: Seizure

Among stroke mimic diagnoses, seizure is one of the most common, being the final diagnosis in up to 20% of stroke mimics.[21,22] For those patients with a prior stroke history, seizures may originate from previous ischemic or hemorrhagic stroke foci.[17] The distinction is less complicated when the patient presents following a witnessed account of seizure activity and has a known history of epilepsy. A constellation of typical symptoms, including generalized convulsions, involuntary movements, postictal confusion, tongue-biting, and incontinence, make an acute ischemic event less likely.[23] The clinical picture clearly is complicated by post-seizure paresis, and in one study this was the most frequent final diagnosis made among stroke mimics that received tPA.[24] Although actual seizure activity is a relative tPA contraindication, more than 8% of patients in one study exhibited seizure activity after acute stroke symptom onset.[25] Previous magnetic resonance imaging (MRI)-based studies have suggested that postictal dysfunction may relate to transient cerebral perfusion mismatch associated with epileptic foci but not with an ischemic lesion in a discrete

Table 2. Vascular Territory and Ischemic Stroke Features	
Anterior cerebral	• Weakness and sensory loss, predominantly in the contralateral leg • Aphasia • Cognitive, behavioral, and emotional disorders may be prominent findings
Middle cerebral (anterior portion involving motor cortex)	• Contralateral hemiparesis • If involving dominant hemisphere: Broca's (expressive or nonfluent) aphasia
Middle cerebral (posterior portion involving sensory cortex)	• Contralateral hemineglect and sensory deficits • Ipsilateral gaze preference • Hemianopia • If involving dominant hemisphere: receptive aphasia
Lacunar (deep penetrating small arteries) — five classic subtypes	1. Pure motor — contralateral weakness, facial weakness, ± dysarthria 2. Sensorimotor — contralateral hemiparesis, hemisensory loss 3. Pure sensory — contralateral sensory loss 4. Ataxic hemiparesis — homolateral ataxia and weakness 5. Dysarthria — clumsy hand — dysarthria, one hand clumsiness, ± central facial paralysis, dysphagia, tongue deviation
Posterior cerebral	• Ipsilateral cranial nerve palsy with contralateral motor and/or sensory defect • Loss of conjugate gaze • Homonymous visual field defect • Wrong way eyes • Deteriorating mental status as observed with basilar artery disease

vascular distribution, as would be seen in a stroke.[26]

Postictal paresis, or Todd's paresis (or paralysis), may be difficult to distinguish from stroke. Reports vary with regard to the incidence and duration, with some studies suggesting that it occurs in as many as 10% of patients with generalized seizures, and may last for several hours or even longer in some cases.[23] However, the vast majority of postictal deficits are commonly short, with one video monitoring study reporting a median time of 174 seconds in the case of focal epilepsy.[27] Deficits may persist longer in the case of generalized seizure, with reports of postictal deficits lasting days. Importantly, focal motor deficits are not the only possible deficit following a seizure. Postictal dysphasia also has been reported to follow dominant hemisphere seizures.[23] MRI with diffusion-weighted imaging (DWI) can assist in the differentiation between acute stroke and prior ischemic event and may provide important information regarding the potential for post-stroke secondary seizure disorder.

Migraine

Migraine headache is a frequent complaint and leads to approximately 1 million patient visits annually.[28] Migraine disproportionately affects females three times as often as males, with a peak incidence around age 40.[28] Patients commonly present with a positive prior history and no evidence of focal neurological deficit on physical exam. However, in the setting of focal neurological deficit, primary headache disorders comprise up to 10% of stroke mimics.[17] For instance, familial hemiplegic migraine is an autosomal dominant disorder with high penetrance. Since this presents with unilateral neurological deficits, it particularly is difficult to differentiate from acute stroke; however, there is a common pattern, since patients tend to be teenagers at the time of onset, and 70% are female.[29] Likewise, migraine in general is thought to have a heritable component; if both parents have a history of migraine, there is a nearly 75% chance a patient will experience the disorder.[30] It is characterized by recurrent severe headaches, classically of a unilateral and throbbing nature. Nausea, vomiting, photophobia, and phonophobia are common associated symptoms. Onset generally is gradual, and headaches may last up to three days.[31] One particular diagnostic challenge is that nearly 30% of acute stroke patients report headache at the time of stroke symptom onset.[32]

Multiple theories have been proposed to explain the phenomenon of migraine headaches. The physiology of migraines is complex, with vasodilatory and inflammatory components. Although some alterations in local blood flow have been noted in patients experiencing migraines, the primary mechanism seems to be a triggered abnormality in the ability of the brain to manage sensory input.[33] There are multiple subtypes that will be described in greater detail later.

Common migraines do not present with aura and are the majority of cases. However, 20% to 30% of migraines are associated with aura and may include a variety of neurological complaints and symptoms.[33] These are known as classic migraines. It is these patients who are likely to raise suspicion for stroke. By definition, migraine with aura is diagnosed after exclusion of organic disease, specifically transient ischemic attack (TIA), ischemic stroke, and intracranial hemorrhage;[31] in some patients with dense focal neurological deficits, this likely requires neuroimaging. Migraine auras generally exhibit a gradual onset over at least five minutes and last a maximum of 60 minutes.[33] Usually, the headache starts within one hour of the aura but may not always occur; it will lack the sudden/maximal onset or thunderclap component attributed to acute subarachnoid hemorrhage. Migraine auras can include a variety of neurological symptoms. Visual symptoms are most common, including scotomas,

flashes/sparks of light, and zigzag-type visual phenomena.[31]

Although less common, paresthesias, motor disturbances, cognitive changes, and language deficits also may be seen in conjunction with aura. Ophthalmoplegic migraine includes involvement of cranial nerves III, IV, or VI with associated eye movement palsies and pupil changes. The third cranial nerve is most commonly involved, and the headache is ipsilateral to the deficits. Retinal migraine may result in scotoma or blindness. In the descriptively named hemiplegic migraine briefly described earlier, the aura includes motor symptoms, such as hemiparesis or hemiplegia. In contrast to many ischemic stroke syndromes, the onset typically is gradual and associated with a visual, sensory, or speech disturbance. Basilar-type migraines present with an aura suggestive of brainstem vascular territory deficits and may exhibit multiple neurological findings, including visual loss (e.g., blindness), dysarthria, tinnitus, vertigo, bilateral paresthesias, paresis, and altered mentation.

In rare cases, an aura may become permanent. If this occurs, and an area of infarct is confirmed by neuroimaging in the distribution of the aura, it is termed a migrainous infarction or migrainous stroke.[31] The pathophysiology of this phenomenon is unclear and remains, thankfully, rare. In the event that a patient with known migraine with aura experiences new or worsening aura symptoms or experiences aura that persists longer than normally would be expected (e.g., > 60 minutes), consider neurology consultation and advanced imaging.

Functional Disorders

Underlying psychiatric disease poses one of the most difficult challenges in the clinical diagnosis of acute stroke vs. stroke mimic, since patients may present with acute motor or sensory weakness in the setting of a specific emotional trigger.[29,34] In particular, conversion disorder is a frequent cause of stroke mimic; in one study it was deemed the underlying etiology in nearly 75% of patients ultimately diagnosed with a stroke mimic who received thrombolytics.[13] Despite this finding, the prevalence of conversion disorder is rare overall, and it essentially is a diagnosis of exclusion not made in the acute care setting. Conversion disorder typically occurs more commonly in women, with the majority of cases seen in early childhood and adolescence. Complaints are widely varied and may include paralysis, aphonia, seizures, ataxia/coordination difficulty, blindness, and anesthesia/paresthesia. Historically speaking, there may be a disproportionate lack of concern relative to the severity of symptoms (la belle indifference). With regard to physical exam, the hallmark is deficit inconsistency observed during serial physical exams, motor-sensory impairments with incongruent vascular territory distribution, and inconsistent task-dependent weakness or "give-away weakness."[17] However, this also has been observed in patients with concomitant organic disease and cannot be used to definitively diagnose conversion disorder.[35] As such, the diagnosis generally is made only following admission and extensive neurological workup.

Functional disorders as a whole are thought to represent a physical manifestation of emotional distress, with common triggers including panic attacks and dissociative episodes.[34,36] Although providers may be tempted to directly confront patients in the acute setting, patients often lack insight into their condition, and the approach may consequently worsen the symptoms. In some cases, providing reassurance to the patient may rapidly improve or resolve symptoms, and if there is an acute stressor identified, then all efforts should be made to remove this from the equation.

Consider an underlying functional disorder if the symptoms are not consistent with a discrete vascular territory, if there are no objective neurological findings, and if there is an inconsistent physical exam. Unfortunately, there is no diagnostic study that can provide this diagnosis reliably. Patients with underlying psychiatric pathology also develop concomitant organic disease, and there are cases of patients being diagnosed with a functional disorder but ultimately found to have organic neurological pathology to explain their symptoms.[35] Providers should be cautious in documenting a non-anatomic exam, atypical presentation, inconsistent physical exam, or a patient's lack of concern about their symptoms as justification for not aggressively evaluating for acute stroke.

Systemic Infections

Sepsis may present with stroke-like features, and the most common associated infection is a urinary tract infection.[37] Commonly associated symptoms include hyperthermia/hypothermia, tachycardia, and altered mental status, with or without an obvious historical or physical exam indication of an infectious source. However, the fact that fever may not be present and that a source etiology may not be immediately obvious during initial evaluation warrants consideration of an acute neurological insult as a potential cause of altered mental status.

In some cases, sepsis is a stroke risk factor, since severe sepsis has been shown to induce a hypercoagulable state.[38] Furthermore, acute infection may result in recurrence of the focal neurological deficits initially present in patients who have a history of prior stroke, even when there is no residual deficit post-rehabilitation at baseline.[39] Alternatively, there also may be cases of acute stroke with concomitant secondary infection, such as aspiration pneumonia.[17]

Obtaining a thorough past medical history, either from the patient or a family member, to establish baseline functional status is crucial but not always possible in the acute setting. When the history is unclear, objective focal neurological deficits should be assumed to stem from an acute neurological insult if history, vital signs, and physical exam do not clearly suggest an underlying infectious etiology. However, the timeframe of symptom onset may add some clarity to the evaluation. Sepsis generally is a gradual process and is less likely to present with the abrupt onset of acute, focal neurological deficits. In addition to more common sepsis sources, infections of the CNS, such as brain abscess, meningitis, and encephalitis, also should be considered in the setting of altered mental status.

Space-Occupying Lesions

Space-occupying brain lesions, including primary CNS tumors, metastases, and abscesses, have been shown to cause stroke-like focal neurological deficits attributed to alterations in cerebral blood flow associated with mass effect.[40] However, mass effect is thought to progress slowly over a 24- to 48-hour period and does not necessarily present

with the sudden, acute change typically associated with an ischemic stroke process.[41] Structural brain lesions are an infrequent cause of stroke mimic, and are subsequently less common than seizure, hypoglycemia, syncope, sepsis, functional disorders, and primary headache.[42] Fortunately, noncontrast enhanced brain computed tomography (CT) can assist in the rapid diagnosis of most acute space-occupying brain pathology, as well as acute intracranial hemorrhage.

Hypoglycemia

Transient hypoglycemia, easily assessed by bedside fingerstick glucose, commonly manifests with acute mental status changes and autonomic symptoms such as diaphoresis and tachycardia. However, it also has long been known to manifest with a constellation of stroke-like symptoms, such as hemiplegia and aphasia, in certain cases.[43]

Hypoglycemia-associated stroke-like presentations have been attributed to a wide variety of etiologies, including insulin or sulfonylurea medication use/overdose and alcohol consumption, as well as less common endocrine sources, such as Addisonian crises and insulinomas.[17,44] When rapidly recognized, hypoglycemia is easily correctable, and patients often quickly improve; however, there are reports of symptoms taking up to several hours to fully resolve.[45] It is very important to address this prior to consideration of tPA administration, and national stroke guidelines mandate that a blood glucose level be obtained prior to tPA administration.[7]

Peripheral Neuropathy

Peripheral neuropathies are caused by cellular-level changes in nerves distal to the brain and spinal cord. In addition to potential toxic-metabolic, ischemic, or inflammatory involvement, the anatomic distribution of these structures relative to surrounding bony and soft tissue structures places them at risk for acute compression and entrapment.[24]

Mononeuropathies may cause focal sensorimotor deficits, and in some instances easily may be mistaken for stroke symptoms when they occur in an acute timeframe. For instance, acute hand weakness may be seen in contralateral cortical strokes that resemble ulnar and radial nerve neuropathy. An acute peripheral nerve injury with subsequent myelin damage may be followed by Wallerian degeneration and result in sensorimotor dysfunction, muscle atrophy, and areflexia.[24]

The history and chronicity of symptoms will aid in distinguishing between acute neuropathy and stroke. However, symptoms associated with acute nerve compression and ischemia may exhibit similar chronicity, and subsequently are more likely to be confused. A high-quality physical exam in addition to detailed history is key to rapidly differentiating between these two entities. Table 3 details common peripheral neuropathy syndromes that can cause significant weakness and thus be confused with stroke.

One common mononeuropathy is radial nerve palsy, which is classically termed "Saturday night palsy." This may occur with prolonged radial nerve compression

Table 3. Vascular Territory and Ischemic Stroke Features

Nerve Involved	Mechanism/History	Signs and Symptoms
Radial nerve compression	"Saturday night palsy" compression of the radial nerve in the spiral groove on the humerus, occurs from sleeping on the outstretched arm, prolonged compression over the back of a chair, etc.	Wrist drop, finger extensor weakness, sensory loss on the dorsum of the hand
Ulnar nerve compression	Most commonly occurs at the elbow due to compression from leaning on a table or similar mechanism	May cause weakness in the interosseous muscles, decreased grip, sensory loss of the fourth and fifth digits
Cervical radiculopathy	Nerve root compression at the neck	Radicular pain is a key feature, specific distribution of weakness will depend on the nerve root C5: Shoulder abduction C6: Wrist extension C7: Wrist flexion C8: Finger flexion T1: Finger adduction and abduction
Lumbosacral radiculopathy	Spinal nerve root compression in the vertebral foramina, herniated disc	Radicular pain is a key feature, deficits will depend on the nerve root L2-4: Hip flexion, knee extension L5: Foot dorsiflexion S1: Leg extension, foot plantar flexion
Common peroneal nerve compression	Compression of the peroneal nerve at the neck of the fibula, leg crossing, squatting, cast	Foot drop, sensory loss on dorsum of foot and lateral shin
Sciatic nerve compression	Compression of the sciatic nerve at the sciatic notch, trauma, prolonged bed rest or seated position, piriformis syndrome	Radicular pain to the back of the thigh and leg, weakness in the lower leg muscles, numbness sparing the medial calf

(as with an arm draped over a chair) or with other prolonged periods of upper extremity immobilization, such as during sleep. Compressive radial neuropathies typically occur distal to the branches that innervate the triceps muscle. Although a patient with radial neuropathy is likely to exhibit weakness with wrist and finger extension, arm extension is expected to remain intact, whereas a stroke patient might have concomitant triceps weakness in addition to the hand and wrist deficits. In addition, radial neuropathy sensory deficit localizes to the hand dorsum, while in acute stroke it is likely to be more volar in nature.[46]

Unilateral Facial Paralysis

Unilateral facial motor weakness is seen in both central and peripheral nerve pathologies. It involves upper motor neurons/contralateral motor cortex lesions or lower motor neurons, respectively. The two pathological foci may be distinguished by a notable difference in the distribution of motor weakness on physical exam. Peripheral lesions (e.g., Bell's palsy) typically manifest as impairment in both upper and lower facial muscle function, whereas central lesions exhibit forehead sparing as the result of bilateral cortical innervation, therefore resulting in intact forehead wrinkling. In addition to differences in the distribution of central compared to peripheral facial paralysis, Bell's palsy also may exhibit additional findings not typically seen in stroke, including decreased tear production (in some cases may also be excessive), acute gustatory impairment, and increased auditory acuity and facial hyperesthesia.[47]

Bell's palsy is the most common cause of unilateral idiopathic facial palsy. It often is preceded by prodromal illness and is commonly attributed to herpes simplex virus infection.[48] It has been more recently associated with Lyme disease in endemic regions. Lyme disease is the most common vector-mediated infection in the United States, is caused by the spirochete *Borrelia burgdorferi*, and is vectored by ticks in the genus *Ixodes*. Bell's palsy represents the most common neurologic abnormality in the second stage of this important disease, and up to 25% of Bell's palsy cases are attributed to Lyme disease.[49] Furthermore, it is responsible for half of pediatric facial paralysis cases in endemic regions.[50]

Vertigo

Acute dizziness is a very common complaint, comprising up to 5% of visits. This represents nearly 10 million such visits annually.[51] Acute dizziness is somewhat open to interpretation and often is described as vertigo, presyncope, and other unspecified unsteadiness in space that persists anywhere from minutes to hours, and often is accompanied by nausea, vomiting, nystagmus, and intolerance with head position change.[52] Acute vestibular syndrome (AVS) presents with these symptoms and generally is presumed to be a viral or post-viral phenomenon. Peripheral AVS generally occurs in the absence of focal neurologic deficits (such as acute unilateral motor and/or sensory deficits and gaze palsy) that would be associated with stroke.[52]

The diagnostic challenge posed in the acute setting is that 35% of posterior stroke cases present with dizziness as the chief complaint, whereas up to 3% of patients with acute dizziness have an ischemic stroke involving the posterior circulation.[53] Ten percent of isolated posterior circulation stroke patients will present with isolated vertigo.[54] However, the vast majority of patients presenting with dizziness are not having an acute stroke, and several groups have reported historical and diagnostic considerations for distinguishing these two entities clinically. Posterior stroke usually manifests with a constellation of neurological deficits and not isolated vertigo.

Vertigo red flags suggesting a potential stroke etiology include any neurological exam deficit, total ipsilateral hearing loss, new ataxia with inability to walk without support, and direction-changing nystagmus.[53] In particular, 71% of patients diagnosed with cerebellar stroke reported acute inability to walk without support.[54] The vast majority of patients with serious pathology underlying their dizziness are older, have multiple cardiovascular risk factors, and have abnormal neurological exams in addition to dizziness, since up to 40% of posterior strokes are attributed to an embolic source.[54]

Thorough neurological examination also helps differentiate between these two disparate causes of dizziness. Ataxia requiring new ambulatory support and direction-changing nystagmus are particularly important in evaluating vertigo, since one of these two signs was seen in 84% of patients with cerebellar infarction and isolated vertigo.[54] Furthermore, performing the Horizontal Head Impuse Test (h-HIT) also may help distinguish between peripheral and central etiologies specifically in the setting of vertigo. The h-HIT is a head acceleration maneuver performed on alert patients with active vertigo and designed to interrogate the vestibulo-occular reflex.[55] It has been well described in the literature and essentially consists of examiner-directed random movement of the patient's head. Patients visually fixate on the examiner's eyes while the head is moved randomly from side to side. A positive test result indicates a peripheral lesion and manifests as a corrective saccade such that as the patient's head is turned away, the patient's eyes initially do not track the examiner but are followed by a rapid visual correction such that the eyes snap back to the original fixation point. Likewise, the lack of a corrective saccade raises suspicion for a central vertigo etiology.

The Head Impulse-Nystagmus Test of Skew (HiNTS), a variation of the h-HIT, approaches 100% sensitivity and 96% specificity for diagnosing posterior stroke when more than one component is abnormal.[53] However, a considerable amount of training is required for diagnostic efficacy with this approach, and a combination of imaging and neurological consultation may be required to differentiate between peripheral and central etiologies. Bilateral peripheral facial palsy is more common with infection.

Neurodegenerative Disorders

Acute demyelinating disorders, as well as initial diagnosis or acute exacerbation of multiple sclerosis (MS), may present with a wide variety of focal neurological deficits, including hemiparesis and cranial nerve or visual deficits.[24] Episodes of acute diplopia, dysarthria, ataxia, and sensory deficits, often exacerabated by warm weather, are common with MS.[56]

Optic neuritis is an acute inflammatory disorder of the optic nerve that may present with sudden unilateral vision loss and occurs more frequently in young adult women.[57] It is a common initial manifestation of MS, occurring in 15% to 20% of these patients. In addition, up to half of MS patients may develop the condition at some point during their disease course.[58]

Acute disseminated encephalomyelitis (ADEM) is a post-infectious or post-immunization immune-mediated demyelinating disorder attributed to transient autoimmune destruction of myelin with multifocal brain lesions visible on MRI that generally occurs within three to six weeks of the inciting event.[59,60] This time course, as well as a wide array of concomitant symptoms, including acute altered mental status, ataxia, optic neuritis, and sensorimotor deficits, aid in distinguishing this from an acute stroke syndrome.

Acute sensorimotor deficits also may be associated with noncompressive transient spinal cord inflammation. Although acute myelopathy is seen in the setting of ADEM, it also may manifest as transverse myelitis.[56,59] This condition generally is not associated with acute back pain, and patients present with a wide variety of acute neurological deficits, including focal sensorimotor weakness and potential impairment of bowel, bladder, and sexual function below the lesion level.[61,62]

Similarly, Guillain-Barré syndrome is an acute inflammatory demyelinating polyneuropathy (AIDP) comprised of several subtypes. Although the less common of these varieties may be difficult to distinguish from acute stroke, it typically manifests as a progressive, ascending bilateral paralysis characterized by peripheral motor weakness, hyporeflexia, and, in advanced cases, respiratory distress when there is compromise of diaphragm innervation.[24] In contrast, acute strokes typically manifest with unilateral deficits as described previously. However, brainstem infarcts in the basilar artery territory may present with a myriad of symptoms, including initial hemiparesis that may progress to bilateral limb weakness or locked-in syndrome, altered sensorium, vertigo, ataxia, bulbar motor weakness with gaze palsies or miotic pupils, as well as so-called "crossed-findings" with ipsilateral cranial nerve deficits and motor or sensory findings on the opposite side.[63,64]

COVID-19 Infection

Although infection with the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) during the global coronavirus disease 2019 (COVID-19) pandemic has been described extensively as causing a constellation of respiratory and gastrointestinal (GI) symptoms, there also have been several reports of focal neurological manifestations associated with the disease.[65-67] In addition to an increased rate and severity of acute ischemic stroke in COVID-19 patients, there have been several cases of stroke mimics.[68]

In particular, language disturbances have been described as early features of COVID-19 disease in some patients.[69] Presenting symptoms have included expressive and receptive aphasia, diminished motor sensory function, transient confusion, and reversible encephalopathy that have occurred both prior to and following the onset of more conventional COVID-19 symptoms. In one case, fever developed following thrombolysis of an otherwise young, healthy individual who presented with focal motor incoordination, aphasia, and confusion that developed rapidly into encephalopathy. Neurological imaging was unremarkable, but lumbar puncture (LP) yielded the uncommon finding of SARS-CoV-2 ribonucleic acid (RNA) present in the cerebrospinal fluid (CSF).[70] In another case, a patient presented with one week of characteristic COVID-19 symptoms but then rapidly developed expressive aphasia that progressed to encephalopathy. Neurological imaging and CSF studies both were unremarkable; however, COVID-19 ultimately was diagnosed per chest computed tomography notable for severe acute respiratory distress syndrome (ARDS).[71] Still another case presented with focal motor weakness and sensory deficits, and like the others, also had unremarkable neurological imaging. In this instance, fever and acute respiratory symptoms developed later, and the diagnosis ultimately was made following admission to a stroke unit.[72]

There are several important considerations for evaluating acute neurological deficits within the context of the COVID-19 pandemic. Language disturbance has been described previously as a potential early feature of COVID-19 infection as discussed earlier. In addition to focal neurological deficits suggestive of possible stroke, it also has been reported that reversible encephalopathy in the setting of COVID-19 may be subacute and fluctuate in severity.[73] In addition to acute ischemic stroke, patients presenting with subacute/acute language deficits, confusion, and encephalopathy in the setting of minimal stroke risk factors may represent COVID-19-associated stroke mimics even in the absence of more characteristic infectious symptoms.

Summary: Approach to Stroke Mimics

Having reviewed common stroke mimics, we now can consider how to approach evaluation of the patient with stroke-like symptoms. It is important to remember that acute stroke likely remains the most life-threatening and time-sensitive diagnosis for patients presenting with acute, focal neurological deficits. With few exceptions, the diagnosis of a stroke mimic will only be made following appropriate resuscitation, laboratory evaluation, and advanced imaging, as well as neurology consultation.

The American Heart Association has developed guidelines for the initial assessment of suspected stroke, and stroke mimics are included in the list of alternative diagnoses to consider during the initial assessment.[7] Recommended ancillary tests are basic blood tests, including serum glucose (rapid fingerstick is initially preferred for expedience), electrolytes, blood urea nitrogen/creatinine (BUN/Cr), complete blood count, troponin, and coagulation studies (PTT, PT/INR, possibly thrombin time [TT] or Ecarin Clotting Test [ECT] if taking direct thrombin inhibitors), as well as 12-lead electrocardiogram (ECG) and oxygen saturation. In most community hospitals, noncontrast enhanced CT scan of the brain is readily available and adequate to rapidly exclude intracranial hemorrhage in a patient eligible for tPA therapy.[7] In specialized stroke centers, emergent MRI may be available to acutely map ischemic brain tissue and provide assistance for reperfusion therapy.

As with all patients, a thorough history and physical exam should be performed in a timely manner, including a baseline National Institutes of Health stroke scale (NIHSS). Two or more of three key symptoms (acute facial paralysis, arm drift, or speech change) are associated with increased odds of having sustained an acute stroke (odds ratio, 5.5; 95% confidence interval, 3.3-9.1). Conversely, the absence of all three of these symptoms is thought to be helpful in identifying patients unlikely to have had an acute ischemic stroke.[74] Particular historical factors have been associated with acute stroke

Table 4. Clinical Questions in the Evaluation of Stroke Mimics	
Age and other demographic data: Is there a high a priori probability of a cerebrovascular event?	Certain demographic and historical factors have been shown to correlate with the likelihood of an event representing a stroke vs. a stroke mimic.
Nature of the symptoms: Positive vs. negative	Stroke is more likely to present with negative symptoms, whereas a mimic due to migraine aura, conversion disorder, or other causes is more likely to have positive symptoms.
Onset and progression	Sepsis may be a slower onset, while seizure, stroke, and even tumor may present suddenly.
Duration	Rapidly resolving symptoms raise the question of a transient ischemic attack or seizure.
Precipitating factors	Deficits preceded by a seizure or illness may indicate an underlying diagnosis.
Associated symptoms, for example, headache, loss of awareness, during or after the attacks	Headache may be associated with stroke but also with migraine. Loss of awareness may increase suspicion of seizure.
Adapted from: Nadarajan V, Perry RJ, Johnson J, et al. Transient ischaemic attacks: Mimics and chameleons. *Pract Neurol* 2014;14:23-31.	

diagnosis in multiple studies, and include older age, higher NIHSS, and a history of atrial fibrillation, hypertension, or diabetes. Likewise, patients who are young, have a low initial NIHSS, are initially unresponsive, have neurological exams incongruent with an anatomic vascular distribution, and patients with a history of epilepsy were more likely to be diagnosed with stroke mimics.[11,13,21,22,39,74-78] One study reported that a history of psychiatric diagnosis was associated with greater likelihood of ultimate stroke mimic diagnosis.[13]

Some stroke mimics are more easily detectable. For instance, if hypoglycemia is identified, correct blood glucose levels and evaluate for functional response. If a space-occupying lesion is noted per noncontrast brain CT (intracerebral hemorrhage, tumor, shift, abscess), tPA is clearly contraindicated, and further diagnostics and treatment should be lesion-specific. If symptoms resolve rapidly and were preceded by a witnessed seizure or there is a history of epilepsy, consider Todd's paralysis as a cause of focal neurological deficits. Although postictal exam findings in the potential unwitnessed seizure that support this diagnosis include tongue biting, bowel or urinary incontinence, and confusion, these objective findings also may be seen with acute stroke in some cases. In the event of a new focal neurological deficit, the initial workup remains unchanged, and if symptoms persist, the patient likely warrants admission with neurological consultation. This type of presentation should be assumed to stem from an acute stroke until proven otherwise. In cases associated with COVID-19, it likely will remain difficult to make the diagnosis without extensive clinical workup, even when there is history consistent with possible SARS-CoV-2 infection.

Specific attention should be given to episodes of prior neurological insult or known pathology, including stroke, seizures, migraine, and mass lesions. If available, a well-documented physical exam is very useful for comparison with a particular patient's clinical picture at the time of presentation. For patients who have sustained a prior stroke, all potential focal neurological deficits should be considered within the context of their medical history, past presenting symptoms, and subsequent residual deficits. Although this information may help provide context for the severity of a patient's symptoms, it is important to carefully consider subjective components of the patient's complaint as well as objective exam findings during surveillance for acute stroke pathology.

Table 4 includes a list of questions for providers to consider when a patient presentation is concerning for transient ischemic attack vs. a mimic.[23] These criteria also can be applied to stroke and may help to develop a differential diagnosis based on symptoms and time course. With any potential stroke patient, frequent reevaluation during the workup is useful both to help clarify the extent of symptoms as well as to monitor for improvement or deterioration. Temporal changes in symptoms over time may gradually move the level of suspicion closer to or farther from acute stroke.

Nevertheless, providers are in a unique position to rapidly identify acute neurological pathology, and it is incumbent on the physician to consider acute stroke first. However, given the wide array of clinical mimics that complicate this process, a detailed understanding of such peripheral entities will enable rapid diagnosis of easily correctable entities (e.g., hypoglycemia) and will expediently resolve exactly which patients are appropriate for acute treatment (e.g., tPA) or require immediate subspecialist support (e.g., neurosurgery) from those for whom a diagnosis of exclusion to explain their symptoms likely will occur during hospitalization.

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CME Questions

1. The American Heart Association stroke guideline identifies one blood test result that is mandatory prior to the administration of tissue plasminogen activator (tPA). This information also is useful in ruling out an important and reversible cause of stroke mimic. Which of the following is it?
   a. Sodium
   b. Prothrombin time/international normalized ratio (PT/INR)
   c. Glucose
   d. Hemoglobin
2. A 73-year-old white female presents with mild confusion and mild right leg weakness after a witnessed fall at home. Her initial National Institutes of Health stroke scale (NIHSS) score is 2, scoring for leg weakness and mild confusion. After quickly reviewing her medical history, she is noted to have a history of hypertension, myocardial infarction, atrial fibrillation, seizures, emphysema, and gout. Which of the following combinations of historical factors would collectively identify the patient most likely to be having a true stroke vs. a mimic?
   a. Female, hypertension, myocardial infarction
   b. Older age, hypertension, atrial fibrillation
   c. Atrial fibrillation, emphysema, seizures
   d. Myocardial infarction, gout, low stroke scale
3. A 38-year-old female with a history of migraine headache and hypertension presents with unilateral face and tongue paresthesias starting four hours ago, followed by a pulsating headache, nausea, and photophobia. She notes a history of similar vision changes prior to her regular headache episodes. Normally this lasts a few minutes and resolves around the time her headache starts, but this time the visual symptoms have persisted. Which of the following most strongly indicates a need for neuroimaging?
   a. Type of aura symptom
   b. Duration of aura
   c. Severity of headache
   d. History of hypertension

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4. Occasionally, tPA is given to patients who are subsequently diagnosed with stroke mimic. Which of the following is true of these patients?
   a. The risk of intracranial hemorrhage following tPA is higher in stroke mimic patients compared with those patients ultimately diagnosed with stroke.
   b. Some of the most common final diagnoses among stroke mimic patients receiving tPA are seizure, migraine, and conversion disorder.
   c. It is very rare that patients given tPA are diagnosed with stroke mimic, occurring in < 1% of tPA patients.
   d. Stroke mimic patients make up an entirely different demographic set relative to stroke patients.
5. In addition to being a risk factor for stroke, sepsis also may mimic stroke by precipitating focal neurological symptoms. What is the most common type of infection to cause stroke mimic?
   a. Space-occupying central nervous system infection (i.e., brain abscess)
   b. Cellulitis
   c. Encephalitis/meningitis
   d. Urinary tract infection
6. Postictal focal neurological deficits (Todd's paresis) may mimic stroke; symptoms may last for minutes to hours, and even longer in some cases. What percentage of patients with generalized seizures will have this manifestation?
   a. < 1%
   b. 10%
   c. 25% to 50%
   d. 50%
7. A 28-year-old male presents with a report of having spent the day at a bar and complains of left hand and wrist weakness with associated paresthesias. Which examination findings suggest a peripheral rather than a central cause of his deficits?
   a. Diminished palmer sensation
   b. Inability to extend the left elbow
   c. Focal weakness with finger and wrist extension
   d. Dysmetria
8. A 27-year-old, otherwise healthy female presents with a history of recurrent prior episodes of diplopia and one day of unilateral vision loss. She reports that the diplopia often has been worse during warm summer days. Her symptoms warrant evaluation for which of the following?
   a. Occipital brain neoplasm
   b. Multiple sclerosis
   c. Ischemic cerebellar stroke
   d. Pituitary adenoma

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