



Stroke Differential Diagnosis - Mimics and Chameleons

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What historical or physical examination findings suggest an ischemic stroke?

What processes may simulate stroke?

What are some unusual stroke presentations?

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Introduction

The diagnosis of acute ischemic stroke is often straightforward. The sudden onset of a focal neurologic deficit in a recognizable vascular distribution with a common presentation - such as hemiparesis, facial weakness and aphasia - identifies a common syndrome of acute stroke. But differential diagnostic problems remain because there are several subtypes of stroke and also because some non-vascular disorders may have clinical pictures that appear identical to strokes. This talk will briefly review the differential diagnosis of stroke starting with stroke sub-types. Stroke “mimics,” non-vascular conditions that simulate stroke, will then be covered in detail. The final discussion addresses unusual clinical pictures that may result from stroke which here are termed stroke “chameleons” - strokes that take on the appearance of something else.

Stroke Subtypes

The abrupt presentation of acute ischemic stroke results from the abrupt interruption of blood flow to a part of the brain. Most commonly this is from embolic or thrombotic arterial vascular occlusion that may be visualized angiographically in many cases when symptoms are severe enough to warrant acute angiography.¹ Other vascular events which may result in stroke syndromes include lacunar strokes, arteritis, arterial dissections, and cortical venous occlusions. Intraparenchymal intracranial hemorrhage from a variety of causes - the spontaneous or hypertensive hemorrhages, vascular malformations, or aneurysmal origin - are frequently encountered clinically and figure prominently in the initial stroke differential diagnosis. These different processes may be considered stroke subtypes for classification purposes and are listed in the first section of Table 1.

The terminology “misclassified” stroke has recently been used to describe patients initially thought to have stroke but later found to have hemorrhage, lacunar infarction, or posterior circulation ischemia after extensive imaging that included magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), diffusion-weighted imaging (DWI), and perfusion-weighted imaging (PWI). One study found that 21% of patients thought to have had anterior circulation ischemic stroke at initial evaluation had other stroke types that had been misclassified.² As more advanced imaging techniques move into clinical practice, diagnostic accuracy of assignment to stroke sub-types will continue to improve.

Stroke Mimics

Background and Studies

Stroke mimic is the term employed for manifestations of nonvascular disease processes when a strokelike clinical picture is produced. The presentation resembles or may even be indistinguishable from an ischemic stroke syndrome. The mimics include both processes occurring within the CNS and systemic events. Distinguishing these noncerebrovascular stroke mimics from strokes is increasingly important in this era of interventional stroke therapies with potential adverse effects.

Stroke mimics may be discovered at different points in clinical investigation; obviously a listing of

alternative diagnoses or mimics based on the initial working diagnosis of stroke after history and physical examination only will differ from final diagnoses when the mimic is discovered after extensive neuroimaging and laboratory work. That many clinical conditions could simulate stroke has been known for years, but studies done with the advent of neuroimaging perhaps allowed the first estimate of the frequency of stroke mimics. One early study of patients admitted with an initial diagnosis of cerebrovascular disease found that 30% had unsuspected intracranial lesions; in all fairness, this included patients with slower progression of neurological impairment (“generalized cerebrovascular disease” was the terminology) as well as more acute presentations.³

A prospective study published 20 years ago reviewed over 800 consecutive patients admitted to a stroke unit from the emergency department of a Canadian hospital.⁴ They found the initial diagnosis of stroke incorrect in 13% of patients. The most common misdiagnosis resulted from unwitnessed or unrecognized seizures with the postictal state being misdiagnosed as stroke in 5% of the study group. Most of these patients had postictal confusion or stupor but transient focal neurological signs were observed in about half of the patients including hemiparesis (Todd’s paralysis), monoparesis, abnormalities of extraocular movements, or hemisensory deficits. Confounding the issue of seizure and postictal state was the fact that almost one-third of the patients in the study with seizures had experienced a previous stroke which made the clinical exclusion of a new stroke difficult at initial evaluation. One patient with presumed postictal confusion and mild hemiparesis was discovered to have non-convulsive 3 cycle/sec spike and wave activity; the confusion and hemiparesis rapidly resolved after intravenous diazepam administration. They also found a small number of patients in their study group admitted with a diagnosis of acute stroke that were eventually shown to have CNS tumors; 1% of the group was discovered to have a neoplasm with primary CNS and metastatic tumors represented in roughly equal numbers. Hemiparesis was of more gradual onset in all of the tumor patients; one-third of the tumor patients presented with seizures. There was also a small miscellaneous group of patients with a misdiagnosis of stroke that included patients with radial-nerve palsy, vertigo, encephalitis, hepatic encephalopathy, and other medical conditions including cardiac failure. One patient with abrupt hemiparesis was a young woman that later developed a relapsing and remitting pattern of weakness typical of multiple sclerosis.

A more recent article by Libman and colleagues looked at variables to determine if they could discriminate between stroke and strokelike pictures.⁵ They looked at consecutive patients presenting to an emergency department with an initial diagnosis of stroke over a two year period. The definition of stroke was the sudden onset of a focal deficit by history or physical examination lasting more than one hour. The initial diagnosis was made by an acute stroke team that consisted of neurologists, emergency physicians, and specially trained nurses; emergency physicians made the initial diagnosis in about 75% of cases. The initial diagnosis was made before computed tomographic study. Both ischemic and hemorrhagic strokes were classified as “true strokes” in their study. Of the slightly more than 400 patients initially diagnosed as stroke, 19% were found to have mimics. Four conditions comprised the majority of the mimics in this study: unrecognized seizures with postictal deficits (17% of mimics); systemic infections (17%); brain tumor (15%), and toxic-metabolic disturbances (13%). There were fourteen other diagnoses, which included positional vertigo, trauma, subdural hematoma, and syncope (see table 2 for full listing). Their analysis showed that decreased level of consciousness and normal eye movements increased the odds of a stroke mimic being present while abnormal visual fields, initial diastolic blood pressure greater than 90 mmHg, atrial fibrillation, and history of angina decreased the odds of mimic being present. With multivariate logistic regression analysis, only decreased level of consciousness was found to be associated with increased likelihood of a stroke mimic rather than a true stroke being present. This

reflects the decreased alertness that may be present with the common stroke mimics of postictal states, infections, and toxic-metabolic disturbances. A history of angina independently predicted the presentation was a bona fide stroke, likely reflecting the association between cerebrovascular and cardiovascular disease.

Kothari and associates reviewed admission diagnosis of stroke (ischemic and hemorrhagic) for over four hundred patients evaluated in an emergency department and admitted to a hospital; they then compared the admitting and discharge diagnoses and found agreement in 96% of cases.⁶ The admitting diagnoses were assigned after CT study and laboratory studies. In this study, there was disagreement of the admitting diagnosis of ischemic stroke or TIA and final discharge diagnosis in 4% of cases (see table 3). Of the patients misclassified at admission as having ischemic stroke or TIA, final diagnoses included paresthesias or numbness of unknown cause, seizure, complicated migraine, peripheral neuropathy, cranial nerve neuropathy, and psychogenic paralysis. They concluded that emergency physicians at this urban teaching hospital could accurately identify patients with stroke, particularly hemorrhagic stroke.

One recent small study used extensive imaging including magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), diffusion-weighted imaging (DWI), and perfusion-weighted imaging (PWI) to investigate patients thought to have anterior circulation stroke. They found that 9% of patients initially diagnosed with stroke were “misdiagnosed” which they defined as completely normal detailed MR studies with a probable alternative clinical diagnosis. The alternative clinical diagnoses included metabolic abnormalities, hemiplegic migraine, psychogenic, and alcohol withdrawal.²

Diffusion-weighted MRI was used to investigate almost 800 patients during stroke-like events in a study by Ay and colleagues.⁷ They found that 3.5 % of the patients with enduring deficits thought to have ischemic stroke had normal diffusion-weighted MRI. Roughly two-thirds of this group ultimately had an ischemic event; ten patients (1.3%) were thought to have stroke mimics, which included migraine, seizures, functional disorder, transient global amnesia, and brain tumor (table 4). Further studies using MRI techniques of diffusion-weighted imaging and perfusion-weighted imaging will undoubtedly be forthcoming.

It is clear that the incidence of stroke mimics in any study depends upon the time that the acute stroke syndrome is assessed. In the study by Libman, when the initial assessment was made after history and physical examination alone, a stroke mimic was present in 19% of cases.⁵ In the study by Kothari, when the assignment of stroke syndrome was made after routine laboratory work and CT scanning, the incidence of stroke mimics was about 4%.⁶ The study by Ay which employed MRI techniques in addition to laboratory work and CT scanning dropped the incidence of mimics to between 1-2%.⁷ There are technical limitations in detecting cerebral ischemia using these techniques, but each intervention, be it laboratory, CT, or MRI, increases the specificity of the diagnosis of ischemic stroke.

Specific Mimics

Hypoglycemia

That transient hypoglycemia may produce a strokelike picture with hemiplegia and aphasia has been known for years.⁸ These patients may be drowsy but are often alert and do not show the more common response to hypoglycemia of confusion, diminished level of consciousness, or coma.⁹ Aphasia may make the history of diabetes more difficult to discover. The syndrome has also been reported in alcoholics with hypoglycemia.¹⁰ The pathogenesis of this focal CNS dysfunction is unclear. Hypoglycemia is generally defined as a blood glucose level of less than 45 mg/dl in these studies. The wide use of bedside rapid laboratory testing for glucose now makes this easily detectable and treatable. The hemiplegia may resolve immediately with the administration of intravenous glucose but resolution over a hours is also reported.¹¹

Mass lesions

Subdural hematoma, cerebral abscess, primary CNS tumors, and metastatic tumors are among the clinical conditions simulating stroke in the studies cited above. The typical clinical presentation of a slowly increasing mass is a progressive syndrome; an abrupt onset of symptoms of these masses seems counter-intuitive. A review of patients with brain tumors presenting to an ED showed that 6% of patients had symptoms that were of less than one day's duration; it was thought that these patients with brief symptom duration might reflect a sub-population who suffer acute deterioration from hemorrhage into the tumor or who develop obstructive hydrocephalus.¹² Secondary effects of mass or edema on cerebral vasculature have been identified as possible causes of abrupt onset of seizures as well. Chronic subdural hematoma has been frequently reported as a cause of stroke and TIA-like symptoms.¹³

Seizures and Postictal States

Every study identifying stroke mimics identifies seizures and post-seizure events as common causes of stroke-like conditions. Traditional thought is that these postictal symptoms are manifestations of seizure-induced alterations in neuronal function that are reversible; structural neuronal alterations are not present. The postictal weakness or Todd's paralysis usually follows partial motor seizures but may follow generalized seizures as well. Duration is usually brief but may last 48 hours.¹⁴ Rare inhibitory seizures with extremity weakness as a manifestation of the seizure event have been reported as well.¹⁴ Seizures may also present as a complication of acute stroke or develop in a patient with a history of stroke.¹⁵ Most studies have identified postictal states indirectly after further seizures were observed or additional history was obtained that suggested a history of seizure disorder.

Migraine mimicking stroke

Migraine may actually precipitate a stroke, but there is also a variant of migraine, hemiplegic migraine, where unilateral hemiparesis outlasts the headache. This is difficult if not impossible to diagnose correctly at first presentation when it must be regarded as a diagnosis of exclusion; only with recurrent, stereotypic attacks can this be suspected. Cases with alternating hemiplegia have

been reported. At times this disorder has been shown to be familial.

Functional Hemiparesis

Little is written about a factitious or feigned stroke yet several studies discover rare patients initially thought to have cerebrovascular disease but later determined to have a functional cause of the hemiparesis or other stroke syndrome. Conversion disorder is the most commonly assigned psychiatric disorder. One study of emergency department presentations of conversion disorder noted that symptoms of paresis, paralysis, or movement disorders were common and were a presentation in almost 30% of patients.¹⁶ They noted significant comorbidity in this population, often other psychiatric disorders, and emphasized that conversion disorder is a diagnosis of exclusion. Patients often undergo multiple diagnostic tests before the diagnosis is assigned.

Encephalopathies and other toxic-metabolic conditions

Hyperglycemia with hyperosmolar state may be associated with focal neurologic deficits simulating stroke but focal seizures are reported in this condition as well. Focal neurologic signs with hyperglycemia may include aphasia, homonymous hemianopia, hemisensory deficits, hemiparesis, unilateral hyperreflexia, and the presence of a Babinski sign.¹⁷ Other metabolic encephalopathies reported to cause strokelike conditions include hyponatremia and hepatic encephalopathy.^{18, 19}

Stroke Chameleons

Strokes with atypical presentations that take on the appearance of other disease process may be termed stroke chameleons, for like the chameleon, these disguised strokes may change and evolve with time. The clinician is left with the daunting problem of discovering the unusual manifestation of an uncommon clinical process. A seemingly infinite number of unusual clinical syndromes have been attributed to ischemic stroke after thorough investigation. The presence of historical risk factors for cerebrovascular disease and the abrupt onset of symptoms may be the best clues available to the emergency physician to detect these unusual stroke syndromes. A few of clinical importance will be briefly summarized.

Most strokes present as a deficit or loss of function. Uncommonly, movement disorders will present from a focal lesion such as ischemic stroke or hemorrhage. Acute hemiballismus, or unilateral dyskinesia, often result from acute vascular lesions in the subthalamic nucleus or connections.²⁰ The movements may vary from wild flinging movements to mild uncontrollable unilateral movements. The key to diagnosis is the abrupt onset of symptoms and risk factors for cerebrovascular disease. A review notes that any kind of dyskinesia, hypokinetic as well as hyperkinetic, may be found from lesions at many different levels in the frontal motor cortical and subcortical regions.²¹

Confusional states, agitation, and delirium have all been reported as a consequence of focal neurologic injury; structures involving the limbic cortex of the temporal lobes and the orbitofrontal regions are commonly involved.²² These states must be distinguished from the neglect syndromes and fluent aphasia in which patients are often reported as confused but careful examination demonstrates a clear focal deficit. Particularly in syndromes of visual neglect, testing for visual fields will reveal a dramatic field cut that the patient cannot report since they are unaware of the deficit.

Sensory complaints of either unusual sensations or loss of sensation are common in parietal and thalamic strokes. At times the sensory manifestation of a stroke may take on the characteristics of another clinical condition. Chest pain and limb pain that mimicked that of myocardial infarction were reported in a small series of patients; most had thalamic strokes but one had a lateral medullary infarct.²³ Sensory symptoms may occur with lesions in many places in the central nervous system; cortical involvement is usually accompanied by other neurologic deficits such as hemiparesis, aphasia, hemineglect, or visual field abnormalities.²⁴

Cortical blindness is unusual but may occur and may be distinguished from bilateral ocular disease by the normal pupillary light responses and normal optic disks. As many as 10% of patients with cortical blindness deny visual symptoms (Anton's syndrome); at times there is an element of "blindsight" where patients retain some remnant visual ability in their blind areas. For example, patients with blindsight may make correct 'guesses' about movements or colors of objects in the visually deficient areas demonstrating some remnant perception of which they are not consciously aware.²⁵

Stroke Differential Diagnosis - Mimics and Chameleons

Summary

The diagnosis of acute stroke remains a clinical diagnosis in the initial phases of patient evaluation. There is a differential diagnostic process to the abrupt onset of focal neurologic deficit that characterizes an acute stroke. “Is this a CNS event?” might be the initial question that is posed by the clinician; the stroke mimics from systemic problems such as hypoglycemia, hyperglycemia, and other encephalopathies should be considered. Certainly consideration of hypoglycemia, common, easily detectable, and correctable, should occur with in every stroke patient encounter. Any witnesses that suggest a convulsive episode should raise suspicion of the presence of an ictal or post-ictal phenomena. Next, if a CNS event is thought to exist, the different stroke sub-types should be considered along with other CNS events that may simulate stroke. The standard acute neuroimaging with non-contrast CT scanning will discover some mass lesions mimicking stroke and confirm a stroke subtype in other patients.

The clinician should also recall that ischemic stroke, like other common diseases, does have uncommon manifestations. Acute stroke should be considered in neurologic syndromes where abrupt onset of symptoms figure prominently, particularly in patients with cerebrovascular risk factors.

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Table 1. Differential diagnosis of acute stroke syndromes, mimics, and chameleons

Stroke subtypes -Cerebrovascular processes resulting in acute stroke syndromes*

ischemic stroke

embolic

thrombotic

hemorrhagic stroke

lacunar infarction

intraparenchymal hemorrhage

intracerebral hemorrhage

arteriovenous malformations

aneurysmal hemorrhage with intraparenchymal extension

venous thrombosis

Stroke mimics--unusual manifestations of nonvascular conditions that may resemble acute stroke syndrome

Metabolic problems

hypoglycemia

hyperglycemia

hepatic encephalopathy

CNS problems

Seizure / postictal

generalized convulsive with postictal confusion or focal neurologic signs

nonconvulsive status epilepticus

hemiplegic migraine

subdural hematoma

abscess

intracranial tumors

primary CNS

metastatic

hypertensive encephalopathy

multiple sclerosis

Psychiatric problems

factitious disorders

Stroke chameleons--Unusual clinical manifestations of strokes and strokes disguised as other clinical processes

acute confusional states

seizures with acute stroke

sensory symptoms

movement disorders

Table 2. Stroke mimics from initial diagnostic impressions in the emergency department (from Libman 5)

Seizure and postictal state
Systemic infection
Brain tumor
Toxic-metabolic
Positional vertigo
Cardiac
Syncope
Trauma
Subdural hematoma
Herpes encephalitis**
Transient global amnesia
Dementia
Multiple Sclerosis Demyelinating disease
Cervical spine fracture
Myasthenia Gravis
Parkinsonism
Hypertensive encephalopathy
Conversion disorder

Table 3. Stroke mimics from ED admission diagnosis following initial neuroimaging and laboratory work (from Kothari6)

paresthesia or numbness of unknown cause
seizure
complicated migraine
peripheral neuropathy
cranial nerve neuropathy
psychogenic paralysis

Table 4. Stroke mimics identified following history, physical, laboratory work, CT scanning, with advanced MR techniques likely failing to show ischemic changes (from Ay7)

migraine
seizures
functional disorder
transient global amnesia
brain tumor

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Annotated Bibliography

1. Norris JW, Hachinski VC. Misdiagnosis of stroke. Lancet. 1982;1:328-331.

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2. Libman RB, Wirkowski E, Alvir J, Rao TH. Conditions that mimic stroke in the emergency department. Implications for acute stroke trials. Arch Neurol. 1995;52:1119-1122.

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They also found 21% of patients thought to have had anterior circulation ischemic stroke at initial evaluation had other stroke types that had been misclassified and were found instead to have hemorrhage, lacunar infarction, or posterior circulation ischemia after the extensive imaging.

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Questions

1. What does the term stroke mimic mean?

- a. A subtype of stroke such as intracerebral hemorrhage that presents like an ischemic stroke
- b. A stroke that mimics another disease
- c. A silent stroke
- d. A clinical condition that presents with the appearance of a stroke

2. How frequently are stroke mimics reported in clinical studies?

- a. 1-2% of initial clinical presentations of stroke
- b. 30-40%%
- c. 50%
- d. 5-20%

3. What factor most likely accounts for the differences that stroke mimics are reported from different studies?

- a. Experience of evaluators
- b. Specialty training of evaluators
- c. Diagnostic tests performed before initial diagnosis is assigned
- d. Patients with witnessed seizures in ED

4. The most common stroke mimics reported in studies include all of the following except....

- a. seizures and postictal states
- b. functional hemiparesis
- c. systemic infection
- d. mass lesions- tumor / abscess

5. Unusual manifestations of stroke include all of the following except—

- a. confusion and delirium
- b. movement disorders
- c. chest pain
- d. all are reported

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Answers

1. Answer d.

The term “stroke mimic” has been used to describe systemic processes that uncommonly present with a clinical picture resembling a common stroke syndrome. Hypoglycemic hemiplegia syndrome is fairly a common example.

2. Answer d.

Depending on the inclusion criteria for the study prior to the assignment of a diagnosis of stroke, mimics are encountered in between 5-20% of patients presenting clinical stroke syndrome.

3. Answer c.

The number of diagnostic tests performed prior to assignment of the initial diagnosis seems explain the difference encountered in the frequency that stroke mimics are reported in different studies.

4. Answer b.

All of the alternative diagnoses are encountered, but seizures and postictal states are the most frequently encountered mimics.

5. Answer d.

All of the answers – confusion, movement disorders, and sensory complaints- have been reported as a manifestation of acute stroke.