Stroke

TOPICAL REVIEW

Stroke Mimics at 30 Years: Where We Have Been, Where We Are Now, and Where We Are Going

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ABSTRACT: Stroke mimics and chameleons remain a major challenge to the clinician and clinical investigator. Misdiagnosis of stroke can result in significant harm to our patients, as well as unnecessary financial costs to the health care systems internationally. The approach to stroke mimics and chameleons has evolved over time with the development of clinical scales and technology. The combination of these tools with clinical acumen can minimize diagnostic errors to the benefit of patients.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: anniversaries and special events ■ diagnostic errors ■ missed diagnosis ■ research personnel ■ technology

The concept of a differential diagnosis has a long lineage tracing from antiquity through William Osler and into the modern era. The development of a differential diagnosis safeguards both physicians and patients from false-positive and false-negative misdiagnoses.[1] Since we coined the term stroke mimics,[2] extensive research has been conducted on medical conditions that resemble stroke symptoms, resulting in false-positive cases. Conversely, there are also cases where the presentation suggests another diagnosis entirely but ultimately proves to be stroke, sometimes referred to as stroke chameleons,[3] leading to false-negative cases. As we reach the 30th anniversary of our publication on stroke mimics, we believe it is valuable to revisit the topic to review where we have been, where we are now, and where we are going.

WHERE WE HAVE BEEN

In our initial study of 411 patients who were diagnosed with stroke on presentation, we found that 81% of them did indeed have a stroke, while the remaining 19% were determined to be mimics. These mimics encompassed 18 distinct conditions, with 5 being the most prevalent: undetected seizures with postictal deficits (17%), systemic infections (17%), brain tumors (15%), toxic-metabolic disturbances (13%), and positional vertigo (6%; Table 1). Decreased level of consciousness with normal eye movements increased the odds of a stroke mimic, while abnormal visual fields, diastolic blood pressure >90 mm Hg, atrial fibrillation on ECG, and history of angina decreased the odds of a stroke mimic. The misdiagnosis of stroke occurs at all phases of the acute stroke pathway, with some studies finding misdiagnosis rate of 28% by emergency medical services or paramedics. In hospitals with an emergency medicine residency or neurology residency, the misdiagnosis rate was found to be 12.5% and 6.3%, respectively.[4,5]

Following the Food and Drug Administration's approval of alteplase for the treatment of acute ischemic stroke, the need for a rapid and reliable differentiation between stroke and conditions mimicking stroke would become increasingly important.

In large hospital-based registries of patients treated with thrombolysis, the percentage of patients diagnosed with stroke mimics has been shown to range between 1% and 16%.[6] In a pooled analysis of 8942 intravenous thrombolysis (IVT)–treated patients, the incidence of symptomatic intracerebral hemorrhage in 392 stroke mimic patients treated with IVT was found to be 0.5%, a significantly lower risk for symptomatic intracerebral hemorrhage compared with IVT-treated patients with

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Table 1. Conditions That Mimicked Stroke

Condition	Frequency, %
Seizure	13 (16.7)
Systemic infection	13 (16.7)
Brain tumor	12 (15.4)
Toxic-metabolic	10 (12.5)
Positional vertigo	5 (6.4)
Cardiac	4 (5.1)
Syncope	4 (5.1)
Trauma	3 (3.6)
Subdural hematoma	2 (2.6)
Herpes encephalitis	2 (2.6)
Transient global amnesia	2 (2.6)
Dementia	2 (2.6)
Demyelinating disease	1 (1.3)
Cervical spine fracture	1 (1.3)
Myasthenia gravis	1 (1.3)
Parkinsonism	1 (1.3)
Hypertensive encephalopathy	1 (1.3)

actual acute ischemic stroke.[7,8] Although the risk of symptomatic intracerebral hemorrhage in patients with stroke mimics is low and should not deter the administration of IVT when stroke is clinically suspected, the administration of IVT is not without cost or harm. A study explored the additional direct and indirect hospital expenses for patients who received IVT, but were subsequently diagnosed with a stroke mimic, and found that the median excess cost for these patients was $5401 per admission.[9] Less well studied are the potential harms to patients, including harms incurred due to delay in arriving at the correct diagnosis, as well as potential psychological burden to patients.[7]

WHERE WE ARE NOW

Seizures

Undetected seizure with postictal deficits and a Todd paresis, in which the patient presents with postictal transient focal weakness, is one of the most common presentations of a stroke mimic. Less commonly, a focal atonic seizure in which the ictal feature is transient focal weakness, typically lasting for a few seconds, can be misdiagnosed as a transient ischemic attack. Further complicating the diagnosis, seizures can also be the initial manifestation of an acute stroke. Electroencephalography is unlikely to be available in the acute setting. In a retrospective study, among 4673 code patients with stroke, seizures were the third most frequent diagnosis among stroke mimics, following peripheral vertigo and metabolic disorders.[10] Seizure onset is known to increase cerebral perfusion in zones of epileptogenesis, and cerebral perfusion rapidly, and transiently, decreases following seizure termination. These changes have been well documented with ictal single-photon emission computed tomography (CT) during presurgical evaluation of patients with epilepsy.[11]

Although CT perfusion is widely used in the evaluation of acute stroke, primarily to identify candidates for mechanical thrombectomy, less is known about its utility in patients with seizures mimicking a stroke. There are several case reports and small studies describing patients presenting with acute onset of focal neurological deficits, ultimately diagnosed with seizures by way of an abnormal CT perfusion scan.[12]

A review examined imaging findings that could help distinguish ictal-interictal perfusion abnormalities from acute ischemic stroke.[10] The primary distinguishing factor that set apart stroke from seizure was the lack of vessel occlusion on CT angiography. Also, in patients with stroke, perfusion abnormalities respected vascular territories, which was not always the case with seizures. It was found that 12.3% of patients experiencing seizures exhibited hypoperfusion affecting multiple lobes or an entire hemisphere. In seizure-related hypoperfusion, the increase in mean transit time and decrease in cerebral blood volume and cerebral blood flow are less pronounced than in the ischemic core in stroke.[10] In postictal patients with Todd paresis, the most common finding was normal perfusion in 54.8%, hypoperfusion in 26.9%, and hyperperfusion in 18.3%. For postictal encephalopathy without focality, perfusion was normal in 72.3%, low in 17.0%, and elevated in 10.6%.[10]

Magnetic resonance imaging (MRI) can also be used to help distinguish stroke from seizure. A systematic review of 20 studies analyzing MRI diffusion-weighted imaging (DWI) changes in patients presenting with seizures found DWI or apparent diffusion coefficient abnormalities in the hippocampus, thalamic/pulvinar region, and in the corpus callosum in most of these studies, as well as varying cortical locations, potentially representing epileptogenic foci (Figure).[13] Arterial spin labeling MRI has also shown regions of hypoperfusion after a seizure that correspond to areas responsible for the negative sequelae seen in Todd paresis.[14]

In summary, while seizures and postictal states represent important stroke mimics, current imaging technology can help distinguish this mimic from stroke.

Peripheral Vertigo

Dizziness and vertigo account for ≈4.3 million emergency department (ED) visits in the United States each year, making up 3.3% of chief complaints in the ED.[15] Over 95% of ED patients with dizziness do not have a stroke. Nearly half of all US ED patients presenting with dizziness undergo CT imaging, despite the low sensitivity of CT in identifying acute ischemic infarcts, especially in the posterior fossa.[15,16] DWI has been shown to miss ≈15% to 20% of acute posterior fossa infarctions <24 to 48

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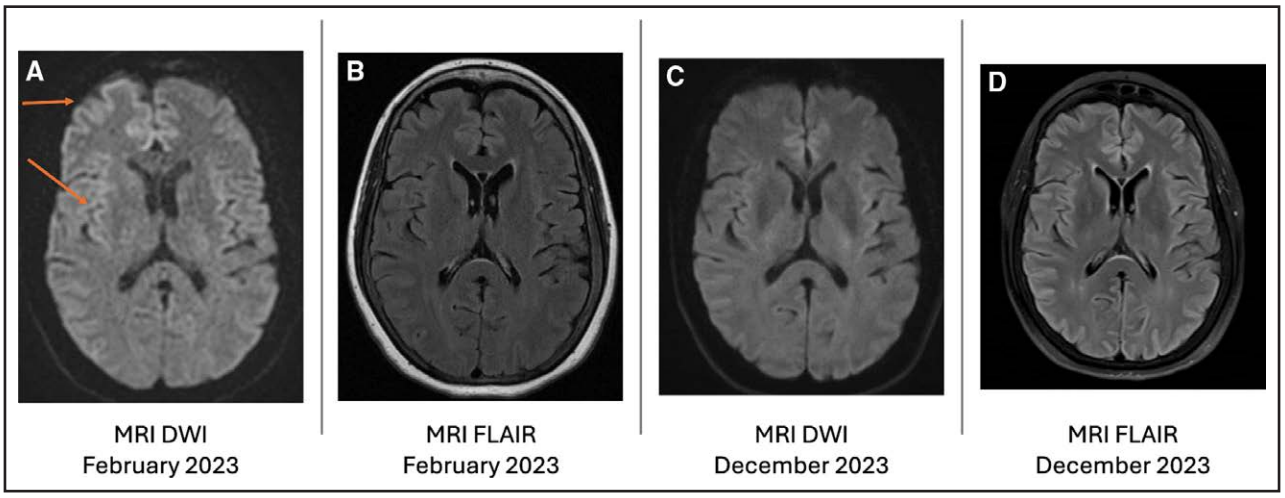

Figure. A 52-year-old woman with a history of epilepsy presented with mild dysarthria and mild weakness of the left arm. Axial diffusion-weighted imaging (DWI; **A**) shows cortical ribboning within the right frontal and right insular cortices and to a lesser extent the left paramedian frontal cortex consistent with a postictal state. Axial FLAIR (fluid attenuated inversion recovery) (**B**) shows no obvious abnormal signal. Follow-up DWI (**C**) and FLAIR (**D**) obtained 10 months later show resolution of cortical ribboning on DWI with unchanged FLAIR signal.

hours from symptom onset, with 1 study suggesting a higher percentage when infarcts are small.[17]

A clinical method for diagnosing vertigo or dizziness at the bedside, based on the most reliable evidence, emphasizes first characterizing dizziness by timing and triggers, then categorizing into 1 of the 3 types: acute vestibular syndrome, spontaneous episodic vestibular syndrome, or triggered episodic vestibular syndrome. Acute vestibular syndrome, most commonly due to vestibular neuritis, can be differentiated from stroke with the Head Impulse, Nystagmus, Test of Skew plus examination plus acute hearing loss, which has been shown to rule out stroke more accurately than early MRI.[15] The differential diagnosis for spontaneous episodic vestibular syndrome includes vestibular migraine and Ménière disease, which can be distinguished from transient ischemic attack with detailed history and physical examination.[15] Finally, the use of the Dix-Hallpike test confirms diagnosis of posterior canal benign paroxysmal positional vertigo in triggered episodic vestibular syndrome.[15]

Described as the bane of the neurologist, dizziness and its frequently described cousin of vertigo remain diagnoses that are treacherous due to the major clinical implications of confusing peripheral vestibular dysfunction with stroke (either as a mimic or a chameleon). While the Head Impulse, Nystagmus, Test of Skew test can be extremely useful as a bedside clinical tool, video-oculography has come to light as an invaluable method for detecting posterior circulation stroke by detailed assessment of ocular motor function, including gaze-evoked nystagmus, skew deviation, impaired smooth pursuit, and saccadic eye movements. A proof-of-concept study encouraged video-oculography to be likened to an ECG for the eyes in 2012 and enrolled 12 consecutive adult ED patients who underwent confirmatory MRI with acute vestibular syndrome. Findings suggested that expert-rated video-oculography–based head impulse test, nystagmus, test of skew examination was 100% accurate (6 strokes, 6 peripheral vestibular).[18] This was redemonstrated in a similarly structured trial a year later by the same group in 22 patients with 100% accuracy that confirmed video-oculography reliability for posterior fossa strokes.[18] Drawbacks to widely implementing this technique lie in the cost of video-oculography equipment and the dearth of subspecialized clinical expertise in the ED. The interrater reliability of this technique during the acute setting has yet to be explored on a large scale.

Migrainous Aura

Symptoms of headache with focal neurological deficits can represent a great variety of pathologies that may be misconstrued as an acute ischemic stroke. Our original article included mimics such as subdural hemorrhage (frequency of 2.6%), brain tumor (15.4%), and demyelinating disease (2.6%), which, while not all inclusive, can include headache as a prominent symptom. While not captured in our original stroke mimic article, migraine presenting with focal neurological symptoms can resemble those of acute ischemic stroke. A separate study concluded that migraine with aura is responsible for 1.79% of all stroke unit evaluations and further represents close to 18% of all stroke mimics treated with thrombolysis.[19] The typical auras of migraine can be characterized as a gradual onset of a mix of positive and negative symptoms that can affect vision, sensation, or language, lasting for no longer than 60 minutes.[20] The paresis of hemiplegic migraines generally lasts <72 hours but may persist for weeks.[21] In addition to clinical history, CT and MRI may also be used to support a diagnosis of migraine with aura. CT perfusion remains perhaps the most dynamic addition to the acute ischemic stroke diagnostic workup over the last decade.

Emergent magnetic resonance perfusion and rapid DWI sequencing studies also represent an advancement in the field but are less widely available in the ED.

A retrospective study compared CT perfusion in patients with migraine with aura and hemiplegic migraine to symptom-matched patients with ischemic stroke. The conclusion was that migraine with aura is usually associated with a perfusion deficit not limited to a specific vascular territory and only a moderate increase of time to peak. Hypoperfusion restricted to a single vascular territory in combination with a marked increase of time to peak or mean transit time may be regarded as unusual for migraine aura and suggestive of acute ischemic stroke.[21] In a separate case series that matched patients with symptoms suggestive of aura with similar symptoms due to acute ischemic stroke, CT perfusion performed within 60 minutes in patients diagnosed with migraine was unremarkable, starkly contrasting with the patients with stroke.[22] These studies suggest patients experiencing migrainous phenomenon demonstrated nonfocal or normal perfusion patterns on CT perfusion.

Similar to CT perfusion, magnetic resonance perfusion-weighted imaging may show defects affecting >1 vascular territory in patients with migraine with aura.[23] Although there have been a few instances where reversible focal diffusion restriction has been found in patients with migraine aura, affecting the splenium, corpus callosum, and cortical regions, more typically, DWI, T1, T2, and T2 fluid-attenuated inversion recovery are found to be unremarkable in acute migraine with aura.[24]

Functional Neurological Disorders

Functional neurological disorders have been demonstrated to represent up to 8% of all stroke mimics.[25] Clinical entities characterized by reversibility and suggestibility previously named conversion disorders can prove vexing diagnoses to make when entertaining stroke in the differential diagnosis. A meta-analysis noted that ≈70% of functional stroke mimics present with lateralized limb weakness and sensory disturbance.[26] In one review, distinguishing between actual stroke and mimic is facilitated by a few examination techniques such as Hoover sign, hip abductor sign, drift without pronation, give-way weakness, and inverse pyramidal patterns of weakness. This review cautions against biases based on sex or age or placing too much emphasis on the presence of panic as it can be present in 64% of patients with stroke. Functional disorders of speech most commonly take the form of stuttering, dysarthria, agrammatism, and a nonfluent aphasia with preserved comprehension and naming. When normal, routine imaging functions to provide evidence against the diagnosis of stroke when there is a mismatch between what imaging suggests and the observed symptoms.[27] Studies suggest being careful to clearly yet tactfully articulate suspicions of a functional neurological disorder to the patient while avoiding terms like hysteria, psychogenic, or conversion disorder.[28]

Transient Global Amnesia

Isolated amnesia as the main symptom of acute ischemic stroke is exceptionally rare and typically proves to be a transient symptom. A retrospective analysis over a 13.5-year period found that patients with ischemic amnesia represented 0.2% of all patients with stroke and transient ischemic attack and were associated with posterior circulation infarction, primarily due to cardioembolism.[29] Fifty-four percent of cases were clinically difficult to distinguish from transient global amnesia, showing that an acute amnestic state can be both a stroke mimic and chameleon. The association of ischemic amnesia and posterior circulation infarcts is related to the posterior cerebral artery distribution, which includes the posterior two-thirds of the hippocampus in addition to the posterior fornix and thalamus.[30] Transient global amnesia is not uncommon and is characterized by isolated anterograde amnesia with a temporary period of retrograde amnesia, typically occurring in adults aged 50 to 70 years with the memory loss lasting usually <24 hours. The etiology of transient global amnesia remains debated with multiple different theories, but most appear to implicate the mediobasal temporal lobe and in particular the hippocampus. One theory is that transient global amnesia may be secondary to cortical spreading depression similar to migraine aura, given that up to one-thirds of patients have a migraine history. Other theories suggest a congestive cerebrovascular or epileptic phenomenon. The fact that punctate DWI and T2 hyperintense lesions without an apparent diffusion coefficient correlate can appear 24 to 72 hours after onset of symptoms in one or both hippocampi adds further complexity to the pathogenesis.[31] Finally, the differential diagnosis includes transient epileptic amnesia, especially if the patient has a history of focal seizures. Retrograde amnesia typically characterizes transient epileptic amnesia, whereas anterograde amnesia is more prominent in transient global amnesia.

Altered Mental Status and Syncope

Metabolic encephalopathy as a stroke mimic (frequency of 12.8% in our original article) may exhibit different CT perfusion patterns, such as preserved or even increased cerebral blood flow and cerebral blood volume, without the characteristic prolonged mean transit time seen in ischemic stroke.[32]

Infection and parainfectious states may also serve as stroke mimics. While direct cerebral infectious states such as meningitis and encephalitis have the potential of causing focal neurological deficits in the form of cerebritis, seizures, subdural empyema, cerebral abscess, or intracerebral bleeding, parainfectious states (urinary

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tract infection, pneumonia) provoking encephalopathy remain more common. The phenomenon of poststroke recrudescence, a clinical entity defined as an acute transient recurrence of previous but recovered focal stroke deficits, often occurs in the setting of parainfectious insult adding ambiguity to the diagnostic picture[33] and further elucidated by Topcuoglu et al[34] by the following criteria: transient worsening of residual poststroke focal neurological deficits or transient recurrence of previous stroke-related focal neurological deficits, identifiable stressors, chronic infarction on brain imaging, absence of acute lesions on DWI, and an unlikely alternative diagnosis. Theories for the cause of this decompensation of functionally compensated structural lesions are many. One theory broadly suggests that some normal neuronal circuitry redundancies are lost focally in diseased brain. From there, the slightest insult to the remaining functioning neurons can produce an amplified response in the form of an echo of prior focal neurological deficits.[35] It is important to distinguish poststroke recrudescence from the century-old concept of diaschisis, which suggests that damage in one focal area of the brain causes a sudden change of function of distant brain regions either through focal neurophysiologic change or nonfocally due to changes in the general strength, direction, and connectivity between brain areas.[36]

In patients presenting with syncope, CT perfusion is typically associated with transient global cerebral hypoperfusion with resulting decreased cerebral blood flow and cerebral blood volume throughout the brain. The perfusion pattern once again shows diffuse changes not localized to a specific vascular territory distinguishing them from the focal perfusion deficits observed in acute stroke.[37] A repeat CT perfusion may reveal rapid recovery of perfusion parameters following the syncopal episode that may be in step with the recovery of consciousness. While syncope does not typically resemble classic stroke, an empirical finding does remain that a small percentage of patients who experience syncopal attacks will demonstrate small acute infarcts on MRI reminding clinicians that these patients warrant scrutiny for subtle exam findings and a low threshold for imaging.[3]

Radiographic Stroke Mimics and Chameleons

In the current era of increasing utilization of neuroimaging, neurologists and radiologists frequently encounter what could be termed radiological stroke mimics. That is, abnormal neuroimaging findings that can be mistaken for acute ischemic stroke. For instance, small punctate hippocampal lesions on diffusion-weighted MRI, most often unilateral and left-sided, are found in up to 85% of patients with transient global amnesia.[38,39] Bilateral, symmetrical T2-weighted and fluid-attenuated inversion recovery hyperintensities involving the medial thalami, mammillary bodies, and periventricular regions of the third ventricle are classically seen in patients with Wernicke encephalopathy. Less frequently, restricted diffusion has also been seen in the acute stage of Wernicke encephalopathy.[40,41] The MRI finding of T2 fluid-attenuated inversion recovery hyperintensities prominently in bilateral posterior cerebral hemispheres seen in patients with posterior reversible encephalopathy syndrome may be difficult to distinguish from bilateral acute ischemic infarction (ie, top of the basilar syndrome). However, the DWI in posterior reversible encephalopathy syndrome is typically hypointense or isointense, usually with increased signal on the apparent diffusion coefficient sequence.[40] Conversely, the radiological stroke chameleon can lead to missing an ischemic stroke, such as finding parenchymal enhancement and misdiagnosing as tumor rather than correctly diagnosing as a subacute ischemic infarct.[42]

Stroke Chameleons

The opposite side of the coin is the camouflaged stroke chameleon. The chameleon represents a presentation that initially is thought to be something other than acute ischemic stroke but is discovered to be just that. It remains important to bear in mind that the same conditions that are often stroke mimics (epileptic seizures, migrainous auras, toxic-metabolic-parainfectious induced encephalopathies, hypertensive urgency) can also serve as a clinical mask for unsuspected stroke thus doubling as chameleons. The frequency of stroke chameleons varies considerably in the literature. A meta-analysis suggested that ≈9% of cerebrovascular events are missed at the initial presentation.[43,44] In our article, 94 patients of 2528 were identified as having stroke chameleons. Among these patients, 31% presented with altered mental status, 16% initially appeared to have syncope, 12.8% had hypertensive emergency, 10.6% had systemic infection, and 9.6% had suspected acute coronary syndrome while a myriad of other presentations constituted the remaining patients.[45] In another study, of all missed cases of ischemic stroke at an academic hospital, 45% of those cases presented within the time frame for IVT.[46]

WHERE WE ARE GOING

Recent clinical scoring tools have been proposed to help identify stroke mimics that need not undergo advanced imaging. The FABS (defined as: absence of facial droop, negative history of atrial fibrillation, age, systolic blood pressure at presentation, history of seizures, and isolated sensory deficit without limb weakness at presentation) scoring system evaluated patients more likely to have a stroke mimic based on 6 variables (absence of facial droop, negative history of atrial fibrillation, age <50 years, systolic blood pressure <150 mm Hg at presentation, history of seizures, and isolated sensory symptoms without weakness at presentation; Table 2) with 1 point

Table 2. Sensitivity and Specificity of Each FABS Scoring System Component to Identify Stroke Mimic

Variables	Sensitivity, %	Specificity, %
Absence of facial droop	94	71
Age <50 y	53	86
Absence of atrial fibrillation	96	17
Systolic blood pressure <150 mm Hg	73	74
Presence of isolated sensory deficit	15	97
History of seizure disorder	14	97

scored for each variable present within 4.5 hours after symptom onset. Involving 784 patients, the study concluded that an FABS score ≥3 in patients with negative CT imaging could identify a stroke mimic with 90% sensitivity and 91% specificity; a FABS score ≥4 had a 98% sensitivity and 45% specificity.[47]

A variation of this tool has been developed, directed toward the ever-growing demand of telestroke services and the need to identify virtual stroke mimics in the form of the TeleStroke Mimic Score.[48] A retrospective study of 1161 video telestroke consults over 9 years generated a scoring system based on the presence of 6 variables, all able to be discerned in the ED (age, atrial fibrillation, hypertension, history of seizure [counted negatively toward the total score], facial weakness, and National Institutes of Health Stroke Scale score >14). Higher TeleStroke Mimic Scores suggested a graded increase in the likelihood of true stroke and decreased likelihood of a stroke mimic; a low score that included lack of facial weakness strongly raised suspicion of a mimic. Similarly, the presence of a seizure disorder raised the likelihood that the presenting symptoms may be due to a mimic in the form of postictal Todd paresis. A validation study of the TeleStroke Mimic Score evaluated the frequency of stroke mimics over 1930 telestroke consults in 3 distinct telestroke networks. Six hundred and thirty stroke mimics were identified resulting in a stroke mimic rate of 32.6%, which mirrored the prior external validation score in the original cohort.[49]

The innovation of mobile stroke units allows for reduction of the time from stroke symptom onset to diagnosis and treatment. In 1 study, stroke mimics were easily detected by the mobile stroke unit teams noting the frequency to be ≈29.3% of all patients, and only 1.6% of those mimics ended up being treated with thrombolysis when evaluated using the TeleStroke Mimic Score.[49] Furthermore, a recent randomized study of 116 patients demonstrated that the triage accuracy of acute stroke including mimics was 100% with mobile stroke units when compared with ≈70% with Los Angeles Motor Scale–based prehospital triage management.[50]

The TeleStroke mimic study also raises questions about the accuracy of stroke diagnosis in the young. It demonstrated that patients with stroke mimics were typically around 10 years younger than those with acute ischemic stroke and often had fewer vascular risk factors. As a caveat, however, another study of young patients compared with older patients found that 60% of young patients with stroke and those with stroke chameleons had ≥1 cardiovascular risk factors. In the group of young stroke chameleon patients, whose diagnosis was missed, the most frequent initial symptoms included headache, neck pain, nausea, vomiting, and dizziness, all notably nonspecific symptoms.[51] The clinical signs that were most often missed in the ED and later discovered by a neurologist included Horner syndrome, subtle focal weakness (monoparesis or hemiparesis), ataxia, nystagmus, and hemianopia, often localizing to the posterior circulation, which remains the most frequent type of misdiagnosed stroke. Misdiagnosed patients were more often women who may present with more ambiguous symptoms such as sensory disturbance, dizziness, and headache and risked being more likely to be deemed psychosomatic, a diagnostic error that, in our opinion, may contribute to health care disparities. Twenty-nine percent of young patients with ischemic stroke were misdiagnosed in the ED, and a meta-analysis on the subject reveals that youth (18–45 years) increases the risk of stroke misdiagnosis as much as 7-fold, and young patients are more likely to present with milder stroke symptoms (lower National Institutes of Health Stroke Scale score) than their older counterparts.[43] To complicate matters further, there may be a risk of overdiagnosis, and there is some cautious and certainly speculative concern that, aside from an actual increased incidence, the reported overall increasing frequency of stroke in the young may be partially secondary to increasing false-positive diagnoses, leading to overestimation of stroke incidence.[52]

Another area of future interest is the use of potential biomarkers to distinguish acute stroke from stroke mimics. These markers of brain tissue damage include glial fibrillary acidic protein, S100B, matrix metaloproteinsase-9, N-methyl-D-aspartate-antibody, and neuron-specific enolase; and circulating apolipoproteins (Apo A_1, Apo C_1, and Apo C_{111}) as but a few candidates that ultimately may serve as point of care tests that could partially replace neuroimaging when triaging patients presenting with acute stroke-like symptoms.[53] S100B, an astrocytic glial calcium binding protein, was one of the earliest neurobiochemicals to be studied in the development of stroke biomarkers. While it had demonstrated some early promise in differentiating acute ischemic stroke from hemorrhagic stroke, and predicting risk of hemorrhagic transformation after IVT, its utility in the setting of an uncertain neurological diagnosis remains to be determined; the molecule can be nonspecifically elevated in traumatic brain injury, extracranial malignancies, as well as in other conditions.[54] When concentrations are measured in the acute setting, matrix metaloproteinsase-9, a gelatinase produced by neurons and glial cells, has been linked to increased infarct size, worse neurological outcome, and complications of hemorrhagic transformation.[55] Matrix metaloproteinsase-9,

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however, is also acutely elevated during epileptic seizures, complicating the picture in the setting of seizures and postictal states mimicking stroke.[56] A panel-like approach has been identified as a potential means to add context to isolated markers drawn in the acute stage of a potential ischemic stroke. A study examined the predictive value of blood biomarkers to aid in stroke diagnosis and concluded that caspase-3 and D-dimer also held promise in distinguishing between acute stroke and stroke mimics.[57] D-Dimer is well-known as a marker for abnormal hemostasis suggesting ongoing fibrin degradation due to thrombus formation and lysis. Higher D-dimer levels are associated with poorer functional outcomes and higher mortality.[58] A recent prospective cohort study of 323 patients with suspected stroke explored the potential utility of assessing glial fibrillary acidic protein and D-dimer levels in identifying strokes due to large vessel occlusions when combined with clinical scoring tools.[59] Validating previously defined levels of glial fibrillary acidic protein and D-dimer at 213 pg/nL and 600 ng/mL, respectively, the study demonstrated large vessel occlusion detection with a specificity of 94% and sensitivity of 71%, and its accuracy improved when blood was drawn <6 hours from symptom onset. Ultimately, if these markers are more widely validated, they will have the most practical value if results can be obtained in the early time window necessary for acute stroke therapy and may help triage patients in the field to the most appropriate stroke center.

As we reach the 30th anniversary of the term stroke mimic, we arrive at a stage where we can take pride in our progress while acknowledging opportunities for improvement. Furthermore, stroke chameleons continue to present a challenge in terms of hidden strokes. As evidence suggests that the typical patient loses 1.9 million neurons each minute in which stroke is untreated,[60] recognizing stroke mimics and chameleons remains imperative and guides appropriate management. Knowing that the cost of false-positive diagnosis of stroke is usually safe for the patient but can be financially and psychologically burdensome, and that the consequences of a missed stroke diagnosis can be debilitating due to missed treatment, the need for greater accuracy persists. Our initial stroke mimic study concluded that the need for diagnostic accuracy was not limited to treating the patient at bedside but for maintaining the integrity of experimental and control groups in clinical trials. The need for rapid and accurate discrimination between stroke and nonstroke endures, and we believe that a combination of clinical skill and evolving tests and technology will pave the way forward.

ARTICLE INFORMATION

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