Errors in the Diagnosis of Stroke-Tales of Common Stroke Mimics and Strokes in Hiding

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Abstract

Introduction: Stroke mimics are some of the common causes of misdiagnosis of stroke, with an attendant surfeit of finances and resources. **Aim:** We attempt to discuss some of the common neurological conditions mimicking stroke in the emergency. **Methods:** We reviewed the articles in English discussing stroke mimics in the last 5 years of publication. **Purpose of the Review:** We discuss the most common causes of stroke mimics encountered in neurological practice. In this short communication, we shall focus on the discussion of the diagnostic pitfalls and clinical clues that will help distinguish mimics from a true stroke.

Keywords: Epilepsy, hemorrhagic stroke, hypoglycemia, ischemic stroke, migraine, mimics, patent foramen ovale, thrombolysis

Introduction

India has covered a lot of ground in recent times as far as the intervention of acute stroke is concerned. Usage of intravenous alteplase (tPA) within 3 h of acute stroke in major tertiary care centers is 7.5% in India versus only 2.4% in China ($P < 0.001$).[1] The pressure to identify strokes as early as possible has led to the emergence of higher number of stroke mimics (SM).[2] India currently has a bleak statistical in-hospital delay time of around 94.17 ± 54.5 mins (median 82 min), a major fraction of the delay being due to the time taken from the imaging to admission in a dedicated unit.[3] As of today, it is the endeavor of stroke neurologists the world over to broaden the population base for stroke thrombolysis. However, this inclusivity has now led to an increase in the thrombolysis of SM.[4] It is to be noted that SM themselves have significant neurological diseases. In a prospective cohort study, the all-cause death of 538 SM was nearly 8% (5.8%–10.6%) when compared with 12.8% in the transient ischemic attack (TIA) group and 16.7% in the stroke group.[5] This outlines the importance of their diagnosis and differentiating them from true strokes. It is also of utmost importance to find the nature of the disease in the stroke mimic to distinguish them from a cerebrovascular event and direct proper treatment toward that direction. Through this communication, we attempt to discuss some common conditions mimicking a stroke in the emergency and discuss pertinent points in their identification and treatment.

Magnitude of the Problem

The aptitude to diagnose and differentiate SM from true strokes varies inversely as the number of hours worked by the emergency physician. It also depends on the qualification and experience of the physician, stroke resident scoring better than an emergency physician in diagnosing stroke.[6] Almost 26%–40% of emergency presentations are mimics, but the proportion reduces consistently as the patients are cleared from prehospital to thrombolysis protocols.[4] Mimics are likely to be younger (67 vs 73 years) and females (59% vs 41%).[2] Nervous system problems are the most common (37%), but conditions affecting almost all other organ systems can be present. While perfusion studies are able to differentiate mimics from true events, some conditions such as epilepsy may even have perfusion deficits accompanying them.[4] In these patients, a proper clinical history and detailed clinical examination are needed. We discuss some of the common neurological conditions that may mimic strokes in the emergency setting.

Methods

We reviewed literature available in English on the common SM published in the last 5 years for inclusion in our article. Our focus remained on the diagnostic aspects of these mimickers in the emergency and the overlap in their clinical and imaging features with a cerebrovascular event. Pertinent articles published regarding some of the established stroke differentials have been included in the study. Isolated case reports of less common or rarer conditions masquerading as stroke are many and have not been taken into account. We have also excluded conditions such as infections and vasculitis that can present as a vascular event due to multiple pathogenetic

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mechanisms (arteritis because of tuberculosis and other infections or vasculitis, bleeds due to systemic coagulopathies or liver disease, etc.).

Epilepsy as a Stroke Mimic

Epilepsy is a common mimicker of stroke that can confuse clinicians. One of the major reasons for the uncertainty is the coexistence of focal deficits coupled with perfusion changes in the epileptogenic foci.[7] Seizures can often present in the hyperacute period of stroke or, occasionally, the stroke itself can present as a seizure. A Todd's paralysis is one of the most common emergency presentations of seizure that mimics a stroke.[8] However, seizures occurring with stroke, apart from their usual associations with ischemic or hemorrhagic strokes, are found in patients who are significantly older, have history of convulsive status epilepticus, and a long duration of complaints. They are also more likely to have premorbid or comorbid structural lesions in the central nervous system (CNS), including old strokes. The latter can present with sudden changes in perfusion associated with a seizure or stroke-like event and can confuse the clinician regarding the management. Antiepileptics are usually beneficial in these cases, and the role of thrombolysis is controversial.[9]

A realistic picture of seizures in stroke was given by a retrospective registry review of 4673 patients admitted with code stroke, of which 2397 (41.3%) presented as SM. Of these, 188 were true seizures and 27 presented with a seizure at onset. Almost 25% (49/188) showed perfusion changes, of which 35 showed hypoperfusion and 14 showed hyperperfusion.[10] In a separate study, contralateral hyperperfusion along with electroencephalography (EEG) changes were seen in patients presenting with seizure as SM. In these patients, EEG was usually fruitful when done within the first 3 h, with a sharp-spike discharge showing association with higher ipsilateral relative cerebral blood flow than the contralateral side.[11]

Functional Stroke Mimic

Psychiatric disorders occupy a large percentage of SM presenting to the emergency. Patients are usually female and have predominant involvement of the nondominant side with somatization symptoms which may be secondary to emotional distress. A larger proportion of these patients are also smokers or people with a risky, stressful lifestyle.[12] Although a fraction of them may have previous strokes and the incident episode maybe a defensive reaction to an adverse emotional event, such episodes are significantly less than patients with medical SM and true stroke. Fleeting neurological signs, suddenness of appearance and disappearance of symptoms, and inconsistency of signs are all clues to a functional rather than a true cause of stroke.[13]

Headache as a Mimicker of Stroke

A headache in itself or as an accompaniment of any other systemic disease can mimic a stroke. There is an interplay of a number of factors in stroke and migraine-like concurrent coronary artery disease, genetic vascular pathologies, and the presence of patent foramen ovale (PFO).[14] The multiple mechanisms explaining the presence of a headache as an SM may be because of cortical spreading depression leading to hemodynamic changes in the cerebral blood flow and increased vascular resistance with the breakdown of neuronal ion homeostasis. The release of inflammatory mediators after the break down causes excessive glutamate release causing cytotoxic cell damage. This is reflected in the form of neuronal deficits due to neuronal necrosis.[15]

Some have postulated the systemic release of inflammatory mediators into the circulation through a PFO as an important mechanism behind occurrence of focal deficits. A PFO is present in 27.2% of asymptomatic population and has a significantly higher occurrence in migraine patients with aura.[14] On the contrary, genetic factors such as methylenetetrahydrofolate reductase C677T, polymorphisms of angiotensin-converting enzyme, and familial hemiplegic migraine (FHM) involving the channels CACNA, ATP1A2, and SCN1A are likely to have no association with occurrence of neurological deficits.[15] The FHM is, in fact, a distinct group of disorders with recurrent neurological presentation resembling a TIA or stroke which usually precede, or sometimes accompany a headache. FHM is significant in that it can cause vasospasm in the vessels, a finding that may complicate the assessment. However, a family history, recurrent episodes of migraine, and neurological deficits associated with a peaking of headache are usually a clue to the diagnosis.[16] It is important to note that several other genes may be implicated in the pathogenesis of a migraine complicating stroke. The common ones are mutations in the collagen gene COL4A1 and NOTCH3 mutation seen in Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and HTRA1 mutation seen in cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL). The presentations are usually with lacunar strokes and diagnosis rests on genetic studies and typical imaging findings on magnetic resonance imaging (MRI) and electron microscopic findings of basement membranes. And other cellular structures.[15]

Metabolic Abnormalities Mimicking Stroke

Disorders of the glucose metabolism are one of the common metabolic abnormalities presenting as a stroke. Focal neurological deficits can be seen in upto 2% among those presenting with hypoglycemia. The main pathology suggested is the presence of cerebral vasospasm leading to a predisposition of neurons to the asymmetric blood flow leading to ischemia.[17] Rapid correction of hypoglycemia usually improves the symptoms.

Tumors as Stroke Mimic

The so-called tumor attacks are said to occur when tumor and other space-occupying lesions present acutely in a stroke-like fashion. The problem with imaging of tumors like glioma is that

the hypoattenuation on noncontrast computed tomography (CT) may be mistaken for a stroke and thrombolysis may be contemplated, with disastrous consequences.[4] Clinicians often miss the contrast enhancement in these masses because noncontrast CT scan is the most common imaging to be done.[18] In addition, intratumor bleeds are occasionally mistaken for intracerebral hemorrhage and may be managed as strokes. However, the intratumoral hemorrhages are often subcortical in location and present a higher cerebral blood flow ratio outside the hemorrhagic tumor component.[19] Careful history showing an evolution period, seizures, and headache are important clues to indicate space-occupying lesions although they may each exist individually in stroke cases as well and a noncontrast CT scan may not be able to diagnose them in the emergency.[20]

Peripheral Vertigo as a Stroke Mimic

Sudden-onset dizziness and vertigo have long been held to be an important stroke mimic, whereas multiple studies have shown the association between isolated dizziness, vertigo, imbalance, and stroke to be very low (3.2%). Of these, only imbalance is a symptom known to be a predictor of a cerebrovascular cause.[21] In fact, the patients with a possibility of stroke were older, more likely to have hypertension, and had at least two stroke risk factors. A useful dictum to remember in these cases is that vertigo and dizziness alone are signs of peripheral vestibular disorders, whereas imbalance without vertigo or dizziness is usually the result of a cerebellar stroke, usually within the superior cerebellar artery distribution.[22]

Other Causes of Stroke Mimic

Apart from these common conditions, cord lesions like demyelination, CNS infections, channelopathies, poisoning, infections, injuries, envenomations, and musculoskeletal conditions can also present with varying amounts of a focal motor and sensory deficit which can be differentiated from the true stroke by proper history and clinical examination.[4]

Safety of Thrombolysis of Stroke Mimic

The biggest concern in the presentation of SM rests on the outcome of thrombolysis. In several studies, SM have shown a post-thrombolysis rate of around 1%–2%, which is far less than what is seen for true strokes.[23] This is because a relatively normal vasculature of SM is far less liable to bleed in response to a thrombolytic in comparison to diseased atherosclerotic vessels.[24] A meta-analysis of nine studies showed the rate of symptomatic intracranial hemorrhage to be 0.5% among 392 SM treated with thrombolysis which had significantly lower risk than in patients with acute ischemic stroke [risk ratio 0.33; 95% confidence interval (CI): 0.14–0.77; $P = 0.01$).[25]

In addition, the percentage of patients with excellent outcomes in thrombolysis is significantly higher in SM when compared with true strokes. Also, the side effects of tPA, especially the incidence of orolingual edema, is significantly lesser in patients with true stroke when compared with SM. Despite this, with the increased number of SM in emergency put up for thrombolysis, the cost considerations of thrombolysis in SM show increased financial burden to health systems.[26]

Differentiating TIA from Stroke

TIAs can often confuse clinicians in their presentation and mimic true strokes. Almost 60% of patients with suspected TIA turn out to be mimickers. However, these transient neurological symptoms, even if they do not meet the criteria of TIA, especially of posterior circulation, may be associated with posterior circulation strokes [odds ratio (OR): 3.07; 95% CI: 1.57–5.82), coronary events, and dementia.[27]

While an urgent MRI showing the absence of diffusion restriction can conclusively prove the nature of TIA, the presence of vertigo, dizziness, falls, and other nonfocal symptoms can give a false impression of stroke mimic. Patients should always undergo a detailed neurological examination and causes of peripheral vertigo must be ruled out. Imaging along with vessel imaging of intracranial and extracranial vessels should be done in every suspected case. Even otherwise, patients with confirmed TIA usually require aggressive management.[28]

Normal Diffusion-Weighted MRI during Stroke

Ischemic regions of the brain show hypoattenuation on diffusion-weighted imaging (DWI) with a corresponding decrease in apparent diffusion coefficient in case of an ischemic brain. The diffusion-restricted region represents the region with cytotoxic edema and neural energy loss. However, occasionally, the diffusion restriction may be absent in patients with a suspected ischemic event. In these patients, it may be an indication of TIA or maybe negative in a true stroke if done early enough in the course of the disease. MRI is usually less sensitive for changes in the brainstem. Leukoariotic changes may also miss an acute event which maybe erroneously counted as an SM. However, it is important not to miss the proportion of them that may still be cases of possible lacunar stroke with negative imaging or cases which may show a diffusion restriction on follow-up imaging. Perfusion studies are usually useful in this regard as they demonstrate perfusion deficits in them.[29] Also important to consider is the phenomenon of reversal of diffusion restriction.

This reversal of diffusion can occur in upto 11% after thrombolysis. This occurs especially in those cases where patients are thrombolyzed within 3 h and in those who do not have proximal occlusion. Also, patients who recanalize within 24 h usually show a reversal of diffusion restriction. The National Institutes of Health Stroke Scale, or NIHSS is a tool used by healthcare providers to objectively quantify the impairment caused by a stroke. It is composed of 11 items, each of which scores a specific ability between a 0 and 4. The minimum score is 0, while the maximum possible score

is 42. Hence, if proper imaging modality is not chosen at the presentation of the patient to the emergency, it would give false impression of having been a stroke mimic despite being a true stroke.[30]

How to Distinguish between Stroke and a Mimic at the Bedside

A call for possible stroke usually involves a sudden disturbance of speech in a quarter of patients, followed by deficits in motor function in approximately 21.9% and disturbance in consciousness in 14.8%.[31] These cardinal symptoms are usually the most significant indicators of a cerebrovascular deficit but may be seen in all the other conditions discussed above. Careful history usually suffices to distinguish a true stroke from a mimic. Of all the presentations, often those with nonfocal symptoms, complaints of a headache, presenting with a seizure at onset, and unable to give the exact time of onset of stroke are usually indicative of stroke mimic.

Patients with true strokes usually demonstrate focal neurological signs such as gaze deviation, hand or leg weakness, cranial nerve abnormalities, visuospatial dysfunction, and cerebellar or brainstem signs. An extensor plantar response is highly useful in such cases to indicate a cerebrovascular dysfunction (OR: 2.61; CI: 1.60–4.27). However, seizure at onset or loss of consciousness does not correlate with the possibility of a stroke.[32]

How to Improve Diagnostic Errors in Stroke

Often, the onus for correct diagnosis of stroke lies on the resident in the emergency services. Errors in stroke diagnosis can arise from prehospital factors including erroneous history by patient's family and poor screening practices. They may also come from lack of emergency detection systems for blood sugar, blood pressure, screening for drug or substance overdose, improper assessment of neurological deficits, and not using clinical decision rules or a proper physical examination.[24] Use of biomarkers would also be a good step toward detecting strokes from mimics. It is also a good exercise to systematically exclude all the contraindications and exclusion criteria before deciding to go ahead with intravenous tPA. As they help eliminate the more common standard mimics from true stroke and help in improving the logistics and expansion of the practice of judicious use of thrombolysis in the emergency department.[33]

Clinical Skills for the Resident

The significance of a proper history and the insistence for timings cannot be overemphasized when dealing with a case of suspected stroke. Ascertaining the exact time of onset of symptoms, the semiology, and evolution of neurological deficits and the progression, if any of the weakness or neurological deficit, are all clues toward diagnosis. Prior medical history, history of migraine and epilepsy, should be always sought. Immediate recording of the vitals with special attention to blood pressure, palpation of pulse, and auscultation of heart sounds should be done in every case of suspected stroke. In the absence of overt weakness, sudden change in personality, language disorders or aphasia, isolated sensory symptoms without motor weakness, skew deviation of eyes, pupillary size and reaction, conjugate deviation of eyes, and gaze preference can hint toward a stroke-like event. Before proceeding with imaging, immediate assessment of metabolites especially blood sugars, cardiac troponins, and electrolytes should be undertaken. Finally, imaging may require additional perfusion studies in addition to acute stroke imaging protocols of diffusion-weighted and fluid attenuated inversion recovery sequences. It is important to remember that despite all skills and laboratory and imaging back-up, certain neurological conditions may be missed despite all attempts to extricate a cause. In the event, it is a reasonable risk to consider thrombolysis in such patients over not thrombolysing them in view of the possible consequences in the future. It is also of paramount importance to treat a stroke mimic rather than leave them untreated in the frenzy of directing efforts at stroke detection and management. This is because every mimic is merely a disease in hiding. Only experience and diligence in clinical practice shall help us not just in differentiating the true strokes from their less obvious counterparts but also in according to the so-called mimics their justifiable need for attention and care.

Conclusion

The number of conditions mimicking strokes in the emergency is quite varied. A thorough clinical history and examination are the essential tools needed to differentiate between the conditions. It is of utmost importance to rule out the exclusion criteria for the use of intravenous tPA in patients presenting with stroke. In doubtful cases, use of EEG and perfusion studies maybe required even in acute-onset focal neurological deficits to differentiate them from a genuine cerebrovascular event. Finally, it is important to regard even the mimics as important pathological conditions by themselves and to treat them accordingly. It is also important to remember the caveats of stroke progression which can have an effect in the interpretation of results.

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Conflicts of interest

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