

Review Article

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Stroke mimics: A review

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Abstract

Acute ischemic stroke is a time-sensitive emergency requiring rapid accurate diagnosis and treatment. Stroke Mimic (SM) is a noncerebrovascular condition that presents with acute focal neurological deficits and masquerades as a real stroke. SMs account for 20-40% of stroke presentations in the emergency department. The purpose of this review is to make a summary of SMs, so that clinicians, especially emergency physicians, can improve their knowledges and make accurate diagnoses and treatment.

Keywords: Stroke mimic; Misdiagnosis; Emergency; Focal neurological deficit.

Abbreviations: SM: Stroke Mimic; AIS: Acute Ischemic Stroke; CT: Computed Tomography; CTP: Computed Tomography Perfusion; MA: Migrainous Aura; FSM: Functional Stroke Mimic; MIDS: Mitochondrial Disorders; HFNS: Hypoglycemia With Focal Neurological Signs; CVST: Cerebral Venous Sinus Thrombosis; HSV-1: Herpes Simplex Virus-1; GBS: Guillain-Barre Syndrome; CIE: Contrast-Induced Encephalopathy; MIE: Metronidazole Induced Encephalopathy.

Introduction

Stroke is the second leading cause of disability and death globally. 87% of them are ischemic strokes [1]. Acute Ischemic Stroke (AIS) is a time-sensitive emergency that requires accurate diagnosis promptly [2]. Rapid treatment of AIS improves outcomes [3,4]. Early alteplase administration is recommended for patients within 3 hours of onset of AIS [4,5]. However accurate early recognition and diagnosis is extremely challenging. Stroke Mimic (SM) is a noncerebrovascular condition that presents with acute focal neurological deficits and masquerades as a real stroke. They account for 20-40% of stroke presentations in the emergency department [3]. Although in most previous studies low risk of complication has been conferred and the overall risk of hemorrhagic complications is low when thrombolysis was used in a SM, unnecessary administration of alteplase may result in patient harm for some individuals [6,7]. Besides, it can not only add needless expense and radiation and contrast exposure from Computed Tomography (CT) but also lead to delayed and inappropriate management. The purpose of this review is to make a summary of SMs, so that clinicians,

especially emergency physicians, can improve their knowledges and make accurate diagnoses and treatment.

Seizure

Some studies show that seizure was the most common causes of SMs, accounting for 17-28.5% [6,8,9], and could also be one of the initial manifestations of acute stroke [7]. It is frequently difficult to make an accurate diagnosis of seizure immediately. Todd's paralysis after convulsive seizures can mimic stroke especially when there is no history of epilepsy [10]. Additionally, it is easily neglected that isolated speech impairment is also a challenging clinical manifestation of SM because it is very rare among adult-onset epilepsy [11,12]. A retrospective study of 72 patients with sudden onset of aphasia admitted for a suspected stroke, done by Polverino P et al, shows that 50 patients were diagnosed eventually as cerebrovascular etiology while 22 patients were diagnosed as epileptic SM [12]. Computed Tomography Perfusion (CTP) is a reliable tool to differentiate acute seizures from acute stroke [13]. A study shows that there were perfusion changes in over 25% SM patients who were diagnosed epilepsy eventually [7].

Migrainous Aura (MA)

The acute-onset of MA can be classified as SM [14]. Nearly 2% of all possible stroke patients evaluated emergently were diagnosed MA ultimately, and about 18% of all SM patients treated with intravenous thrombolysis were diagnosed MA finally [15]. A retrospective study that reviewed the 10-year medical records of patients treated with acute stroke management protocol shows as follows: Among those MA patients presenting with SM, Sensory and brainstem auras were the most common auras followed by motor, visual, and verbal deficits. These auras were difficult to differentiate from stroke sometimes [16]. CTP and susceptibility-weighted imaging may be useful to distinguish them [14,17]. A study shows that a novel CTP-based quantitative tool which used mean transit time, Cerebral blood flow, and cerebral blood volume parameters could be helpful to differentiate MA from AIS [18].

Functional neurological disorders

Functional neurological disorder which has also been defined as conversion disorders is a common SM [19]. A case of a SM patient who was treated with intravenous alteplase on four separate occasions in four different hospitals and was finally diagnosed as Functional Stroke Mimic (FSM) was reported by Liberman et al [20]. Compared with stroke, FSMs were younger, showed a higher prevalence among female, had a lower socioeconomic status, received less education, were more frequent in developing countries, and presented more with weakness/numbness but less with reduction of consciousness or verbal deficits [21,22]. FSMs often present with dramatic physical signs and symptoms [23]. Hoover's sign was very specific for the diagnosis of functional weakness [24].

Metabolic diseases

Some metabolic diseases can mimic stroke. Mitochondrial Disorders (MIDs) can present SM in both clinical manifestations and imagings. Of various MIDs, particularly of mitochondrial encephalopathy, lactic acidosis, and stroke-like episode syndrome, stroke-like episodes are a common phenotypic feature and stroke-like lesions are a unique feature which can change their appearance over time [25,26].

Hypoglycemia with Focal Neurological Signs (HFNS) in patients with diabetes mellitus, especially type 1 can be SM [27]. Because it may also display a hyperintense lesion by DWI with decreased values on the ADC map, it is hard to be distinguished from AIS. Disproportionally small lesion in contrast to neurological signs may be helpful for differentiation [28]. Glucose correction treatment can be effective [29]. CTP might be helpful to discriminate HFNS from AIS, but further evidence is still needed [27]. Hyperosmolar hyperglycemic state which is a life-threatening complication of type 2 diabetes can also mimic strokes for the reason that it often presents with neurological symptoms [30]. Early CT and/or MRI can be useful in such circumstance. Nonketotic hyperglycemia-associated chorea can be misdiagnosed as stroke and it can give a hemorrhagic stroke alert because of false-positive interpretation of CT [31]. It is recommended that MIDs such as hypoglycemia should be taken into consideration in all suspected patients no matter whether they are known to have diabetes or not [32].

Vascular diseases

Vascular diseases may mimic stroke sometimes. Cerebral Venous Sinus Thrombosis (CVST) can present with stroke-like syndrome [33]. Patients with CVST have a higher risk of thrombolysis-related intracranial hemorrhage compared to other SMs [34]. Diagnosis is often delayed due to its nonspecific clinical manifestations [35]. MRV venography, CT venography, and DSA is useful for the confirmation of the diagnosis of CVST [36].

Some special diseases can mimic stroke such as intracranial idiopathic acute epidural hematoma [37], spinal epidural hematoma [38-40], and aortic dissection [41,42]. But intravenous thrombolysis can lead to disastrous result for these diseases. Besides, some case reports show that internal carotid artery dissection [43], basilar artery aneurysm [44], Squamous cell carcinoma of the neck [45], and acute thrombotic occlusion of subclavian artery can also mimic stroke.

Infections

Infections can play a role in the pathogenesis of stroke in some circumstances probably by triggering a latent pro-thrombotic state or damaging the vascular endothelium. They can also occur as stroke-like syndromes which may be hard to make a correct diagnosis immediately. Treatment of stroke or stroke-like syndromes of infectious origin with alteplase administration can be related to a higher hemorrhagic risk and a more extension of the ischemic lesion [46]. Herpes Simplex Virus-1 (HSV-1) encephalitis can mimic stroke when it occasionally shows the development of unilateral brain MRI lesions with extensive cytotoxic edema [47]. Detection of HSV-1 DNA in the cerebrospinal fluid can confirm its diagnosis. Additionally, varicella zoster meningitis [48], tick-borne encephalitis [49], and cephalic tetanus can mimic stroke according to some case reports.

Creutzfeldt-Jakob disease is a rare fatal human prion disease and its annual incidence is about one per million [50,51]. It has various initial symptoms and may mimic a stroke during its early stage [52]. But it is characterized by rapidly progressive dementia and neurologic degeneration that is often followed by behavior disorders, ataxia, myoclonus, and akinetic mutism [50,52]. Parasitic encephalopathy may present as SM and initial brain CT scan may suggest AIS sometimes. But personal history, parasitic serology, MRI, and antiparasitic treatment can be helpful in differentiation [53]. In addition, Streptococcal pneumoniae meningitis secondary to acute mastoiditis, Escherichia coli meningitis, and Pseudomonas meningoencephalitis had also been reported mimicking stroke in the previous literatures [54-56]. COVID-19 infection may present as a stroke, also it can mimic a stroke even there is no respiratory syndrome at all [57-60]. Detection of SARS-CoV-2 in Cerebrospinal Fluid is important in such circumstances. HIV type 1 infection may also mimic SM sometimes [61].

Immune diseases

A retrospective study shows that there were 6 cases presenting with hemiparesis/stroke-like episodes among 24 patients diagnosed as Anti-N-methyl-D-aspartate encephalitis [62]. Guillain-Barre Syndrome (GBS) is characterized by symmetrical limb weakness and are flexia, but it can have various initial manifestations some of which may mimic stroke [63]. Miller-Fisher syndrome, is a variant of GBS. Triads of ataxia, are flexia and ophthalmoplegia are its characteristic features which may

mimic posterior circulation stroke [64,65]. Susac's syndrome is characterized mainly by encephalopathy, hearing loss and branch retinal artery occlusions. However its initial stroke-like symptoms may be not the aforementioned feature [66]. Myasthenia gravis may mimic stroke, but it has the characteristics of atigability and diurnal variation [67-69]. Besides, fulminant inflammatory demyelination and anti-MOG antibody-associated disorder can mimic stroke sometimes [70,71].

Malignant tumors

Brain malignant tumors may mimic stroke sometimes while they are absolute contraindication for thrombolysis therapy [72,73]. They are rarely seen on a brain non contrast CT scan. The mismatch between neurologic examination and CTP may suggest a SM in some cases [5]. Intravascular large B-cell lymphoma may mimic stroke [74]. It is difficult to be diagnosed when it is limited to the central nervous system. Biopsy can confirm the diagnosis [75].

Toxicity, and medication side effects

Since alcohol intake is one of the risk factors for stroke [76], it's difficult to differentiate acute alcohol toxicity from stroke sometimes. Alcohol toxicity can mimic a posterior stroke because they have the similar symptoms such as dysarthria, gait disturbance and nystagmus. A prospective observational single-center study shows that of all patients presenting as suspected stroke, 6% also drank alcohol, 1% was diagnosed as acute alcohol toxicity (accounting for 7% of the SMs) [77].

Contrast-Induced Encephalopathy (CIE) may present as SM clinically and subarachnoid hemorrhage radiologically [78-81]. CTP and EEG may be helpful in the differentiation between CIE related SMs and stroke [79].

Toxicity of lamotrigine which is a antiseizure medication may mimic stroke because it can share symptoms such as vertigo, ataxia and diplopia with posterior circulation stroke. Concentration of it is an effective way to reduce the risk of misdiagnosis [81].

Methotrexate encephalopathy can present with stroke-like symptoms. But the rapid reversal of MR abnormalities in parallel with neurological symptoms contribute to its diagnosis [83,84]. Metronidazole Induced Encephalopathy (MIE) can also mimic stroke. It has the clinical features of cerebellar dysfunction, altered mental status and extrapyramidal symptoms [85]. The classical manifestations of MIE on MR are as follows: the splenium of the corpus callosum shows T2 hyperintensity and the dentate nucleus and/or brainstem shows symmetric T2 lesions [86].

Toxicity of some other medications such as 5-Fluorouracil [87], anesthetic and transdermal scopolamine exposures [88,89], and acetazolamide may mimic stroke according the published literatures [90]. Bismuth-related acute neurotoxicity can lead to SMs as well as toxicity of Stramonium, tetrahydrocannabinol edible ingestion, abuse of nitrous oxide and so forth [91-94].

It is of great importance to take a careful medical history, alcohol history, medication history, occupational history and exposure history so as to diagnose such patients correctly.

Hereditary diseases

It has been reported that some types of Charcot-Marie-

Tooth could present as SMs [95,96]. So it is essential to make a careful family history assessment, physical examination, nerve conduction studies, MRIs and genetic testing in order to make a accurate early diagnosis. Other cases of unusual hereditary diseases such as hereditary angioo-edema with C1 inhibitor deficiency type I, and atypical glutaric aciduria type I have also been reported [97,98].

Other diseases

Various cerebral diseases can present as SMs. It has been reported that posterior reversible encephalopathy syndrome, central pontine myelinolysis, grey matter heterotopia, and cerebral lymphomatoid granulomatosis can mimic stroke. The clinical features of Parkinson's disease are usually asymmetrical at presentation and so it can be misdiagnosed as stroke initially [99-103]. Meningioma can also mimic a stroke when it compresses the premotor cortex [104].

Some neurologic symptoms caused by many diseases such as thyrotoxic hypokalemic periodic paralysis, hepatic encephalopathy, paraneoplastic cerebellar degeneration, and transient headache, neurological deficits and lymphocytic pleocytosis in the cerebrospinal fluid can mimic stroke sometimes [105-108].

Conclusion and prognosis

Not all focal neurological deficits are strokes actually. SM should be considered in the differential diagnoses of AIS with atypical presentation even in fast-paced settings. The range of SM diagnoses, unclear differentiating clinical features and the short treatment window for AIS bring many challenges for early identification. It is vital to be alert to SMs. Further studies on refining triage and transport of suspected acute stroke may be useful. It is hopeful to reduce the misdiagnoses of stroke by extensive knowledge of brain vascular anatomy, differential diagnoses for stroke, detailed collection of medical history, careful physical examination, and comprehensive evaluation of suspected manifestations. Special techniques of assistant examination methods, and development of effective tools to predict SM are also expected in the future.

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