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Clinical Review

STROKE MIMICS AND ACUTE STROKE EVALUATION: CLINICAL DIFFERENTIATION AND COMPLICATIONS AFTER INTRAVENOUS TISSUE PLASMINOGEN ACTIVATOR

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☐ **Abstract—Background: Intravenous tissue-plasminogen activator remains the only U.S. Food and Drug Administration-approved treatment for acute ischemic stroke. Timely administration of fibrinolysis is balanced with the need for accurate diagnosis. Stroke mimics represent a heterogeneous group of patients presenting with acute-onset focal neurological deficits. If these patients arrive within the extended time window for acute stroke treatment, these stroke mimics may erroneously receive fibrinolytics. Objective: This review explores the literature and presents strategies for differentiating stroke mimics. Discussion: Clinical outcome in stroke mimics receiving fibrinolytics is overwhelmingly better than their stroke counterparts. However, the risk of symptomatic intracranial hemorrhage remains a real but rare possibility. Certain presenting complaints and epidemiological risk factors may help differentiate strokes from stroke mimics; however, detection of stroke often depends on presence of posterior vs. anterior circulation strokes. Availability of imaging modalities also assists in diagnosing stroke mimics, with magnetic resonance imaging offering the most sensitivity and specificity. Conclusion: Stroke mimics remain a heterogeneous entity that is difficult to identify. All studies in the literature report that stroke mimics treated with intravenous fibrinolysis have better clinical outcome than their stroke counterparts. Although symptomatic intracranial hemorrhage remains a real threat, literature searches have identified only two cases of symptomatic intracranial hemorrhage in stroke mimics treated with fibrinolytics.** © 2015 Elsevier Inc.

☐ **Keywords—stroke mimic; stroke; fibrinolysis; thrombolysis; hemorrhage; hemorrhagic transformation; symptomatic intracranial hemorrhage; safety; tissue plasminogen activator; tPA**

INTRODUCTION

Since the landmark National Institute of Neurological Disorders and Stroke (NINDS) study in 1995, intravenous tissue plasminogen activator (IVtPA) remains the only treatment approved by the U.S. Food and Drug Administration for acute ischemic stroke (AIS) within the extended 4.5-h time window (1). Earlier treatment and recanalization is clearly associated with improved mortality and clinical outcome due to prevention of neuronal ischemia (2,3). However, the timely manner in which AIS must be treated can result in patients without AIS erroneously receiving IVtPA. This heterogeneous group, presenting with acute-onset focal neurological deficits that are later found to have nonvascular etiologies, has been termed stroke mimics (MIM). Across all studies, MIM treated with IVtPA have significantly better clinical outcomes than their AIS counterparts. This review highlights four clinical questions pertaining to MIM: 1) defining MIM, 2) diagnosing and identifying MIM, 3) defining MIM etiologies, and 4) management of MIM after imaging confirmation.

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DISCUSSION

Defining Stroke Mimics

Stroke mimics: heterogeneous definition and caseload per institution. Rates of MIM treated with IVtPA—ranging from 1.4% to 16.7%—vary widely by institute. Although numerous papers have cited MIM and their characteristics, lack of uniformity in defining AIS and MIM may be one reason for these heterogeneous rates (4–6). MIM classification ranges from purely clinical diagnosis to imaging confirmation with magnetic resonance imaging (MRI). With recent literature questioning the accuracy of diagnosing diffusion weighted imaging (DWI)-negative imaging as "aborted strokes," rates of MIM treated with IVtPA may actually be under-represented (7). Classification of MIM and aborted strokes based on clinical and radiological criteria remains ongoing and will likely shift reported rates of MIM treated with IVtPA.

Caseloads of AIS and IVtPA administration also factor into rates of MIM treated with IVtPA. In general, higher MIM rates are found in larger volume stroke centers. Four single-center studies with MIM rates of 14%, 10.4%, 7%, and 6.5% yielded average yearly treatment rates of 102.4 patients/year for 5 years, 89.3 patients/year for 6 years, 81.4 patients/year for 4 years, and 92.6 patients/year for 7 years, respectively (8–11). Conversely, smaller-volume centers are associated with lower rates of MIM. An institute's function as a primary stroke center vs. a tertiary referral center for "drip-and-ship" IVtPA cases can also affect MIM rates. One tertiary center with mostly drip-and-ship IVtPA cases reported a MIM rate of 16.7% (120 patients/year for 1 year) (12).

Symptomatic intracranial hemorrhage after IVtPA. As shown in Table 1, although the majority of studies did not report any instances of symptomatic intracranial hemorrhage (SIH), the risk of SIH remains a real and potentially destructive complication of IVtPA (8,9,11–15). A meta-analysis with IVtPA use in myocardial infarction reported an SIH rate of 0.94% (16). However, these early studies with myocardial infarction and IVtPA are difficult to compare due to differences in dosing (with higher amounts of fibrinolytics used in myocardial infarction) and oftentimes more aggressive concomitant use of therapies, such as heparinization and aspirin, which are typically withheld in current guidelines for IVtPA use in stroke (16).

In fact, extensive literature searches for SIH in MIM treated with IVtPA yielded only two cases. One case report demonstrated SIH after IVtPA use in a patient with glioblastoma multiforme (17). And finally, a large multicenter study showed SIH rates of 1.0% (one patient with seizure) in MIM treated with IVtPA (18). Despite these low rates, SIH still remains possible, necessitating identification of MIM and avoidance of IVtPA.

Table 1. Compilation of Stroke Mimic Etiologies Receiving IVtPA and Complications

Stroke Mimic Diagnosis	Hemorrhagic Conversion (Post IVtPA)	Other Complications
Seizure (8–15,18)	Yes	None
Tumor (9,11,14,17,18)	Yes	None
Complicated migraine (8–12,14,15,18)	None	None
Benign paroxysmal positional vertigo (9,14,15,18)	None	None
Alcohol intoxication (9,14,18)	None	None
Psychiatric (depression, anxiety, conversion disorder) (8–14,18)	None	None
Myocardial infarction (9,14)	None	None
Drug toxicity (9,14)	None	None
Bell's Palsy (9,12,14)	None	None
Hypoglycemia (9,10,12,14,18)	None	None
Syncope (8)	None	None
Sepsis (12)	None	None
Dementia (11)	None	None
Spinal cord lesion (epidural abscess, spinal hematoma) (8,18)	None	None
Meningitis (8)	None	None
Encephalitis (15,18)	None	None
Heat stroke (8)	None	None
Demyelinating disease (9,10,14,15,18)	None	None
Brachial plexopathy (18)	None	None
Sinusitis (10,18)	None	None
Amaurosis fugax (9,14)	None	None
Rheumatoid arthritis (9,14)	None	None
Appendicitis (9,14)	None	None

IVtPA = intravenous tissue plasminogen activator.

Diagnosis and Identification of Stroke Mimic

Diagnosis. The diagnosis of AIS vs. MIM depends on several factors: presenting complaint, epidemiological factors, onset time of focal neurological deficit, presence of anterior vs. posterior circulation vascular distribution, and available imaging modalities for stroke evaluation. A summary of some of the factors favoring AIS vs. MIM are provided in Table 2.

Presenting complaint. Presenting complaint can often indicate whether a clinical syndrome represents AIS or MIM. One study evaluated presenting complaints and found only three could be used to differentiate AIS from MIM: paresthesia (odds ratio [OR] 10) and chest pain (OR 16.7) identified MIM, whereas focal unilateral weakness (OR 4.15) identified AIS. Other presenting complaints—including altered mental status, aphasia, isolated facial droop, dizziness or vertigo, visual field