Review

Stroke mimics in the era of thrombolysis

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Abstract

Stroke thrombolysis has emerged as a valuable treatment for acute ischaemic stroke in the first 4.5 hours after symptom onset. The need for rapid initiation of treatment and the small but inherent risk of life-threatening side effects requires a high degree of diagnostic accuracy with only limited time for investigation. It is widely recognized that a significant proportion of patients presenting with "stroke-like" symptoms will in fact have an alternative diagnosis – so called stroke mimics. There has been anxiety that wrongful treatment of stroke mimics could be harmful. This paper reviews the published data on the incidence of stroke mimics and the outcome of thrombolysis in these cases. We conclude that the risk of adverse outcomes from thrombolysis in these cases appears to be minimal on the available evidence and is certainly significantly less than the potential harm that could result from denial of, or delay in administration of thrombolytic therapy.

Index words: stroke mimics, thrombolysis

Introduction

A significant proportion of patients presenting with stroke like symptoms will be found to have an alternative diagnosis other than ischaemic stroke. These conditions are known as "stroke mimics". Stroke mimics can be difficult to distinguish from true ischaemic strokes acutely. With the advent of thrombolysis and other interventions for acute stroke, identifying stroke mimics has become a major diagnostic challenge. If thrombolysis is performed in a patient with a stroke mimic, however what is the risk of complications? Clinicians embarking on establishing a stroke thrombolysis service may have considerable anxiety that they are using a treatment that carries significant risk of life threatening side effects. This may lead to denial or deferral of treatment while further investigations are performed with the result that valuable time is lost and any benefit from thrombolysis is significantly reduced. The clinician in this dilemma might well ask, "Is this anxiety justified?" Published data now goes some considerable way to answering this question and enables increasingly safe, rational decisions to be made in the emergency room when time pressures are challenging.

Epidemiology of stroke mimics

Stroke mimics usually require extensive neuroimaging and laboratory work up to confirm the diagnosis. Studies in patients who were not thrombolysed show that the prevalence of stroke mimics varies from 1.3% to 25%[1,2]. Further studies suggest the rate of misdiagnosis of acute stroke by US emergency physicians ranges from 5% to 33%[3]. More recent studies have estimated that the prevalence of stroke mimics ranges from 3% to 13% in patients treated with tissue plasminogen activator [4,5,6,7,8,9]. The prevalence of stroke mimics varies greatly between the different studies reflecting the diagnostic criteria and imaging modality used. The lower prevalence of stroke mimics in recent studies may be due to better clinical and imaging criteria. Some of the earlier studies used clinical criteria and CT with only a few patients having a MRI[1,3] while in later studies[4,5,6,8,9,10] all patients were subject to a MRI scan. Efforts to increase the availability of acute treatment of stroke while concurrently reducing the time for thrombolysis increases the likelihood of stroke mimics receiving treatment. The prevalence of stroke mimics varies depending on the diagnostic criteria used. For example, patients considered to have acute cerebral ischaemia but with no supporting evidence for stroke on subsequent imaging have been classified as neuroimaging negative cerebral ischaemia and may account for more than one quarter of stroke presentations[6,10].

Differential diagnosis of stroke mimics

In clinical practice the commonest causes of a stroke mimic presentation are post-ictal paralysis, complex migraine and psychogenic conversion disorder. Other rarer causes include hypoglycaemia, cerebral tumour or abscess, sub-dural haematoma, metabolic encephalopathy, Uhtoff's phenomenon in multiple sclerosis and transient global amnesia[1,6,8, 9,10,11]. The relative frequency of these diagnoses varies between studies. Post-ictal paralysis accounts for between 19.6-38%, complex migraine between 19.6-37% and psychogenic weakness 21-26.8%[4,6].

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Clinical history and examination with appropriate investigations, particularly brain MRI with DWI will identify stroke mimics ultimately, but in the emergency room the clinician may have to depend on clinical assessment alone as tests are not possible within the thrombolysis time window. Certain clinical findings may be helpful, however. Hand et al[1] have demonstrated that cognitive impairment and abnormal signs in other systems suggested a stroke mimic. They also noted that the following suggested a stroke: an exact time of onset, definite focal symptoms, abnormal vascular findings, presence of neurological signs, being able to lateralize the signs to the left or right side of the brain, being able to determine a clinical stroke sub classification.

A more recent study[9] showed that aphasia and accompanying convulsions were commoner in mimics. Known cognitive impairment, aphasia and accompanying convulsions were independent predictors of stroke mimics.

Outcome of thrombolysis in stroke mimics

Several studies have looked at outcomes in patients presenting with a stroke mimic who receive thrombolysis [4,5,6,7,8,9,10].

One of the earliest of these looked at 151 patients of whom 6 had a final diagnosis other than stroke. If TIA was also included into the definition of stroke mimics the number increased to 10[7]. This group suffered no harm from thrombolysis and overall had less disability as measured by the modified Rankin Scale (mRS) at discharge.

Six further more recent studies have documented excellent functional outcomes in patients with stroke mimics who received thrombolysis with no cases of cerebral haemorrhage[4,5,6,8,9,10]. This is as expected, bearing in mind that the most common causes of stroke mimics are conversion disorders, migraine and seizures. Furthermore there were no cases of orolingual oedema and the overall outcomes were good in the stroke mimic group. The largest more recently available data come from the Helsinki Stroke Thrombolysis Registry, which looked at the outcomes of 985 consecutive ischaemic stroke patients from 1995 to 2008. This also addressed the issue of outcomes in neuro-imaging negative stroke patients who are given thrombolysis[10]. They identified 14 stroke mimics (1.4%), 275 neuro-imaging negative strokes (28.3%) and 694 neuro-imaging positive ischaemic strokes (71.5%). There were no significant differences between the patients with neuroimaging negative ischaemic strokes and stroke mimics with regard to medical history or clinical features except that stroke mimics were younger with a mean age of 55.5 years (45-59) vs70 years (59-77) in acute ischaemic strokes. Of the stroke mimics none had haemorrhagic complications, while 6 (2.2%) in the neuroimaging negative group had haemorrhagic complications. An excellent outcome was more common in stroke mimics and neuroimaging negative group at 3 months[10].

Overall the results of these studies are reassuring although it is acknowledged that the absolute numbers of stroke mimics is small and so the data should still be interpreted with caution. It is important also to note that all of the studies used recombinant tissue plasminogen activator as the thrombolytic agent and these results cannot be extrapolated to the use of other thrombolytic agents. Table 1 gives a summary of findings of these studies.

Table 1. Summary of the most recent studies on stroke mimics and thrombolysis

	Study details	*Stroke mimics (SM) identified*	*Characteristics and outcome of stroke mimics*
Guilan et al 2012	Total number 621 patients Stroke mimics 15 (2.4%) Based on CT and MRI Few had multimodal CT	Somatoform disorders Headache with neurological deficits and CSF lymphocytosis Herpes encephalitis Glial tumours Migraine with aura Focal seizures Cerebral venous thrombosis	SM were younger, had lower baseline deficit, fewer vascular risk factors and predominantly left hemispheric symptoms. Good outcome with no symptomatic ICH or disability (functional outcome at 3 months mRS >2) Use of intravenous thrombolysis appears to be safe in SM with favourable prognosis.

(Continued)

	Study details	*Stroke mimics (SM) identified*	*Characteristics and outcome of stroke mimics*
Forster et al 2012	Total number 648 patients Stroke mimics 42 (6.49%) Based on MRI	Seizures Conversion disorder Dementia Migraine Brain tumour	Cognitive impairment, aphasia and accompanying convulsions were independent predictors of stroke mimics. Orolingual angioedema occurred in one patient. None had intracerebral bleed or deteriorated clinically.
Artto et al 2012	Total number 985 patients Stroke mimics 14 (1.4%) Based on CT and MRI	Conversion disorder Encephalitis Epilepsy Demyelination Migraine	Stroke mimics were younger and had less severe symptoms at base line and better 3-month outcome. Stroke mimics were more likely to be females. None developed symptomatic ICH. No difference in medical history or clinical features.
Tsivgoulis et al 2011	Total number 539 patients Stroke mimics 56 (10.4%) Based on CT and MRI	Conversion disorder Complicated migraine Seizure	Stroke mimics were younger and had milder baseline stroke severity. No cases of symptomatic ICH. 96% of the stroke mimics were functionally independent at hospital discharge.
Chernysher et al 2011	Total number 512 patients Stroke mimics 69 (14%) Based on CT and Multimodal MRI	Seizure Complicated migraine Conversion disorder Aseptic meningitis Epidural spinal mass Heat stroke Syncope	Stroke mimics were younger and had a lower baseline deficit. Median discharge NIHSS was 0. Median length of stay in hospital was 3 days. None had symptomatic intracerebral haemorrhage. Overall outcome was good.
Winkler et al 2009	Total number 250 patients Stroke mimics 7 (2.8%) Based on CT and MRI	Seizures Conversion disorder Non convulsive status due to glioblastoma multiforme	Stoke mimics had a lower baseline disability. None of the mimics had orolingual oedema or intracerebral haemorrhage Stroke mimics had a favourable outcome.

Conclusion

The currently available data indicate that intravenous thrombolysis does not adversely affect the favourable natural history of stroke mimics. The benefit of treatment with tissue plasminogen activator for patients presenting with an acute stroke episode would not seem to be negated by the potential for harm to patients presenting with stroke mimics or imaging negative stroke. The available evidence (even allowing for the low incidence of stroke mimics) suggests there is no justification for withholding treatment in the patient presenting with a clinical picture of acute stroke whilst further investigations, such as DWI, MRI imaging, are obtained, if this would lead to a delay in treatment. Imaging prior to thrombolysis is only to exclude a haemorrhage, not to identify stroke mimics. The clinical features that might suggest a stroke mimic, as well as a younger age and female gender are not sufficiently robust to enable the clinician to make a safe decision on avoiding thrombolytic treatment in the emergency room.

The extremely low rates of adverse events and excellent functional outcomes in stroke mimics however, should reassure clinicians to give thrombolytic therapy for stroke and not withhold it based on the sole concern that the patient's neurological symptoms may be attributed to a stroke mimic.

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