Exclusion Criteria for Intravenous Thrombolysis in Stroke Mimics: An Observational Study

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Background: Stroke mimics (SMs) are frequent in emergency departments (EDs), but are treated infrequently with intravenous recombinant tissue plasminogen activator (rt-PA) thrombolysis. We aimed at identifying the factors that lead to the exclusion of SMs from thrombolytic therapy. *Methods:* Consecutive patients presenting to the ED between December 2004 and March 2011 with symptoms that suggested acute ischemic stroke were included. *Results:* Eight hundred forty-two patients were included in this study; 113 (13.4%) were considered SMs; these patients were younger ($P = .01$), more frequently diabetic ($P = .001$), arrived later to the ED ($P = .03$), had lower National Institutes of Health Stroke Scale scores ($P < .001$), and higher frequencies of negative diffusion-weighted imaging studies ($P = .002$). The most common causes of cases of SM were toxic metabolic disorders (n = 34 [30.1%]) and seizures (n = 22 [19.5%]). The most frequent cause of consultation was aphasia (n = 43 [37.6%]). SM patients had a total of 152 contraindications for rt-PA, with 34 (30%) patients having >1 contraindication. The most frequent of these were being beyond the therapeutic window for thrombolysis (n = 96) and having deficits not measurable by the National Institutes of Health Stroke Scale or very mild symptoms before the start of rt-PA (n = 37). Twenty-four (21.2%) patients had both contraindications simultaneously. Two patients (1.76%) in the SM group were candidates for rt-PA but did not receive this treatment because they or their family rejected it. Of 729 stroke patients, 87 (11.9%) did receive rt-PA. *Conclusions:* SM patients frequently had exclusion criteria for systemic thrombolysis, the most frequent being presenting beyond the established thrombolytic window. **Key Words:** Stroke—stroke mimics—thrombolysis.

In emergency departments (EDs), 5% to 30% of patients initially suspected of having an acute stroke end up with a diagnosis of stroke mimic (SM). Seizures, migraine, psychogenic disorders, and toxic/metabolic causes are the most common nonvascular conditions mimicking stroke.[1-9] They may present with symptoms, such as aphasia, that are classically related to stroke,[5,9] and they may occasionally have abnormal diffusion-weighted magnetic resonance imaging (DWI) scans.[10] Similarly, genuine ischemic strokes may present with normal DWI in the ischemic brain regions that are causing the clinical deficit if these are small or consult too early in the ED.[11]

Thrombolytic therapy is associated with a better prognosis in acute ischemic stroke[12,13]; however, this

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treatment should not be used in SM and may increase the risk of brain haemorrhage.[14] Despite the high frequency of patients with SM presenting to EDs, they receive thrombolytic therapy rather infrequently for reasons that have not been properly evaluated.[5,6]

The aim of this study was to determine the variables associated with the low frequency of recombinant tissue plasminogen activator (rt-PA) treatment in patients with SM.

Methods

In this prospective study, all patients with suspected acute ischemic stroke who presented to the ED of the Clínica Alemana de Santiago between December 2004 and March 2011 were evaluated by the neurologist on call within the first 15 to 30 minutes. After this clinical evaluation, stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS), blood samples were obtained, and an electrocardiogram was performed. Patients were then subjected to a previously described stroke imaging protocol[15] consisting of a computed tomographic (CT) scan of the brain and, in those without contraindications (kidney failure, allergy to contrast media, or an implanted pacemaker), a spiral CT angiography (CTA) scan of the intracranial arteries and then DWI. If CTA was contraindicated, patients underwent magnetic resonance angiography (MRA). In addition, patients arriving with 24 hours of symptom onset were frequently evaluated with transcranial Doppler (TCD) imaging during the acute period. Patients who in the opinion of the attending physician were candidates for intravenous thrombolysis (rt-PA) were treated as soon as possible and monitored with TCD if an arterial occlusion was detected according to the combined lysis of thrombus in brain ischemia using transcranial ultrasound and systemic t-PA (CLOTBUST) protocol.[16] Our institutional thrombolysis protocol followed that established by the National Institute of Neurological Disorders and Stroke (NINDS) trial[12] regarding inclusion and exclusion criteria, and a few weeks after the publication of the results of the third European Cooperative Acute Stroke Study (ECASS III) trial our time window was expanded from 3 to 4.5 hours.[13]

The diagnosis of SM was based on the presence of focal acute or subacute neurologic symptoms with no demonstrable ischemia or arterial occlusion on neuroimaging and normal brain imaging on follow-up (>24 hours later) if performed. A definite alternative diagnosis explaining the patient's initial symptoms must have been made before discharge.

Stroke was diagnosed in patients with history, clinical examination, and evolution typical for vascular brain damage with signs of brain ischemia on CT/DWI in our stroke neuroimaging protocol or on follow-up imaging or if a vessel occlusion was observed in the symptomatic territory.

All stroke study data were extracted from the Clínica Alemana Acute Stroke Registry (RECCA). This is a prospective database that was begun in our institution in 1997 for quality control of the stroke program and includes clinical assessment (NIHSS score), imaging (brain CT, CTA or MRA, DWI, and digital subtraction angiography), time from symptom onset, vascular territory, risk factors, treatments, complications, and outcome. It was approved by the Ethics Committee of Universidad del Desarrollo-Clínica Alemana de Santiago, which also approved this study protocol. Because patients were deidentified, no specific informed consent was required.

Statistical Analysis

We compared the demographic, clinical, and neuroimaging characteristics of patients with SM to those with concurrent stroke in the RECCA database. The Student *t* and Fisher exact tests were used to compare continuous or discrete variables as appropriate. We calculated the number of exclusion criteria for rt-PA in SM patients according to the NINDS study protocol for the patients seen between January 2004 and October 2008 and according to NINDS and ECASS III for those seen after October 2008. All calculations were performed with SPSS software (version 14; SPSS, Inc, Chicago, IL).

Results

Between December 2004 and March 2011, 842 patients with a suspected ischemic stroke were admitted in our centre. Of these, 729 had a definite diagnosis of ischemic stroke, and 113 (13.4%; 95% confidence interval [CI] 11.2-15.9) had a diagnosis of SM. Table 1 compares the baseline characteristics of these patients. Those with SM were younger, arrived later to the ED (mainly after the first 180 minutes), had lower NIHSS scores, (mainly below 5), and were more frequently diabetic; they also suffered less frequently from hypertension and had higher numbers of negative DWI studies. Of the patients with SM, 12 (10%) were classified initially as cases of stroke with symptoms lasting >24 hours and negative DWI studies. All patients had clinical deficits, with NIHSS scores of >8, and 10 of them had some cortical symptoms, such as aphasia resembling middle cerebral artery stroke on arrival to the ED. The other 2 patients with vertebrobasilar symptoms had NIHSS scores of 19 and 24, respectively. Table 2 lists the most common etiologies in the SM group, which included metabolic encephalopathies (30.1%), seizures (19.5%), and migraine (10.6%). Of the patients with metabolic encephalopathies, 33% had severe hyponatremia (<120 mEq/L). Figure 1 presents a case of SM. Table 3 shows the main symptoms for which SM patients arrived to the ED, with aphasia being the most frequent (37.6%) followed by symptoms mimicking posterior circulation deficits (27.5%).

Table 1. *Baseline characteristics and comparison between strokes and stroke mimics*

	Stroke mimics N = 113	Stroke N = 729	OR (95% CI)	*P* value
Mean age, y (SD)	67.1 (14.66)	71.1 (16.2)		.01
Female, n (%)	63 (55.7)	359 (49.2)	1.4 (0.9-2.0)	.1
Time to ED, min (median)	492 (20-5760)	180 (18-7200)		.03
<180 min (%)	17 (14.7)	195 (28.4)		
<270 min (%)	23 (20.4)	229 (31.4)		
Mean admission NIHSS (SD)	4.7 (±3.3)	7 (±6.7)	2.3 (1.5-3.5)	<.001
NIHSS <5, n (%)	76 (67.3)	344 (50)	0.9 (0.5-1.4)	<.01
NIHSS 5-10, n (%)	24 (21.2)	172 (25)	0.8 (0.5-1.4)	.6
NIHSS >10, n (%)	13 (11.5)	171 (25)		.7
Hypertension, n (%)	41 (36.3)	461 (63.2)	0.47 (0.27-0.67)	.001
Diabetes mellitus, n (%)	74 (65.5)	150 (20.6)	2.04 (1.3-2.1)	.001
Hypercholesterolemia, n (%)	27 (23.9)	216 (29.6)	0.74 (0.5-1.1)	.2
Tobacco, n (%)	26 (23)	140 (19.2)	1.25 (0.77-2.1)	.4
Ischemic heart disease, n (%)	31 (27.4)	236 (32.4)	0.65 (0.4-1.0)	.08
DWI performed, n (%)	103 (91.5)	609 (88.6)	1.8 (0.9-3.5)	.08
DWI positive, n (%)	3 (2.6)	551 (90.4)	0.09 (0.03-0.028)	.002
EV thrombolysis, n (%)	0 (0)	87 (12.6)		<.001

Abbreviations: CI, confidence interval; DWI, diffusion-weighted magnetic resonance imaging; ED, emergency department; EV, intravenous; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SD, standard deviation.

In the group of patients with a final diagnosis of SM, a total of 152 contraindications for rt-PA were present; 77 patients had only 1 contraindication, 28 had 2, 5 patients had 3, and 1 had 4. Table 4 shows the contraindications in the SM patients in relation to the use of thrombolytic treatment. The most frequent were presenting to the ED outside of the established time window and clinical deficits not measured by the NIHSS or minimal symptoms before the start of intravenous infusion; 24 (21.2%) patients had both contraindications simultaneously. Only 2 patients in the SM group were candidates for rt-PA, and none of them received this treatment because they or their family refused it. Had these 2 patients received thrombolysis, the proportion of thrombolyzed SM patients would have been 1.76% (95% CI 0.2-6.2).

Of the 729 ischemic stroke patients, 87 (11.9%; 95% CI 9.6-14.5) received rt-PA; of these, 12 (13.8%) had normal initial CT and DWI-MRI scans. In turn, 8 of these had arterial occlusions in the initial CTA or TCD, and in 3 cases evidence of ischemic changes were observed in studies after 24 hours. A 37-year-old patient without vascular risk factors was treated as having "stroke" with an initial NIHSS score of 17; his initial imaging protocol and vascular studies were normal and he experienced a complete recovery during the treatment. Follow-up imaging studies after 24 hours were also normal. No alternative discharge diagnosis was formulated. If we had classified this patient as a SM, we would have had 2.62% (95% CI 0.54-7.5) of SMs as candidates for rt-PA, with 0.9% (95% CI 0.02-4.7) of them receiving this form of treatment.

There were 3 positive DWI studies on SMs; these patients were a woman who was later shown to have herpetic encephalitis and 2 other patients who had a white matter disease and a very small high-grade brain tumor, respectively. These 3 patients had lesions that were positive according to their DWI studies but that did not follow a vascular distribution. The neuroradiologist considered that the images were not compatible with a diagnosis of stroke.

Follow-up brain imaging studies were performed in 58 of the SM patients after 24 hours (CT scans in 25 and MRI scans in 33 cases), none of which revealed images compatible with the diagnosis of stroke.

Discussion

Over a 6-year period, almost 1 out of every 7 patients (13.4%) who presented to our ED with symptoms suggestive of acute cerebral ischemia received an alternative diagnosis. Despite these high numbers of SM diagnosed, similar to those described in other publications,[1-4] the number of SMs who were candidates for thrombolysis

Table 2. *Etiology of patients arriving to the emergency department with stroke mimics*

Etiology of stroke mimics	n (%)
Toxic metabolic disorders	34 (30.1)
Epilepsy	22 (19.5)
Migraine	12 (10.6)
Neuroinfective disorders	11 (9.7)
Peripheral vertigo	7 (6.2)
Conversion disorders	5 (4.4)
Brain tumors	4 (3.6)
Other diseases	18 (15.9)

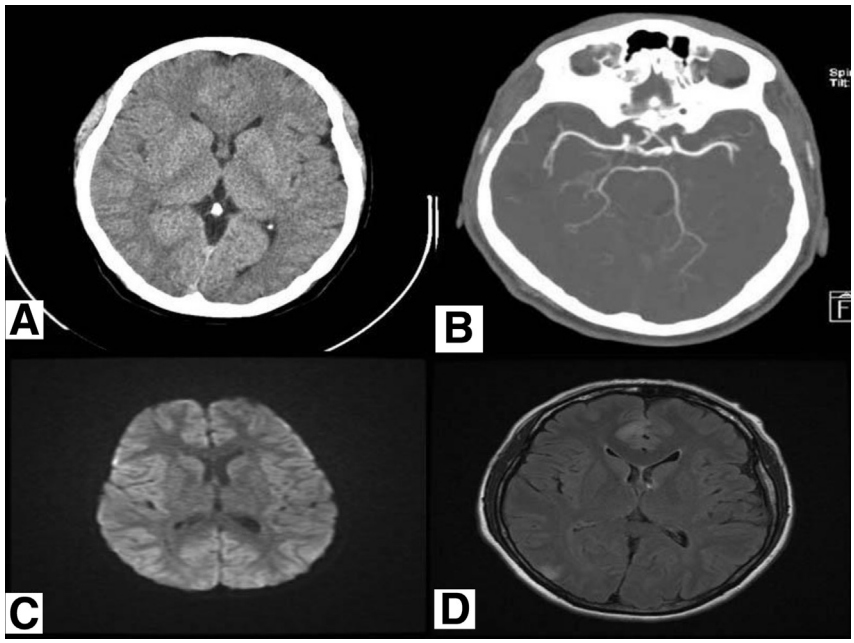

Figure 1. *A 79-year-old white woman with a history of untreated atrial fibrillation woke up and was confused and had left hemiparesis. She arrived at the emergency department 750 minutes after symptom onset. Her initial National Institutes of Health Stroke Scale score was 11 and (*A*) a computed tomographic scan of her brain revealed no abnormalities. (*B*) A computed tomographic angiography scan did not reveal arterial occlusions or stenosis. (*C*) A diffusion magnetic resonance imaging scan was normal. Five hours after being hospitalized, she became febrile and developed seizures. Intravenous aciclovir, antibiotics, and steroids were started and a spinal tap was inflammatory. (*D*) A magnetic resonance imaging scan 24 hours later revealed encephalitic lesions in the right frontal and occipital lobes. She was discharged with a diagnosis of viral encephalitis.*

in our center was low (range 1.83-2.75%), and had they accepted rt-PA we would had 2.2% to 3.3% of thrombolyzed patients who were finally diagnosed as SM, a number that is close to the 2.8% of SM patients thrombolyzed by Winkler et al[5] and the 3.5% reported by Uchino et al,[6] who also found that this number could be as low as 0.8% in comprehensive stroke centers.

The reasons why SM patients are excluded for rt-PA have not been properly evaluated; in our experience, they usually had ≥1 exclusion criteria for the use of rt-PA, the most frequent criteria for exclusion being their late arrival to the ED (mainly after 270 minutes), which could be explained by the fact that in our patients the most frequent cause of SM (30.1%) were toxic metabolic disorders (including 3 cases of sepsis), slightly more than were reported by Hand et al[2] who detected these disorders in 25% of their patients. In our experience, a significant number of the cases were associated with severe hyponatremia, a condition that frequently causes neurologic manifestations, many of them focal.[17] Contrary to ischemic stroke, where an arterial obstruction causes immediate metabolic derangements in the affected tissues,[18] toxic metabolic disorders slowly alter the neuronal environment with changes in water, electrolyte, amino acid, and excitatory and inhibitory neurotransmitters that induce neuronal dysfunction and focal symptoms.[19] This slow manifestation of focal neurologic symptoms causes their late arrival to ED and the subsequent exclusion of rt-PA; this explains why during the >7-year study period more than 1000 patients with metabolic toxic encephalopathies were seen in the ED and only 34 (<4%) were interpreted as strokes. The predominance of toxic metabolic conditions as causes for SM explains why diabetes mellitus is frequent in this group of patients. In addition, neuroinfectious disorders, which represent 10% of our SM cases, also have a gradual beginning, with focal symptoms becoming evident in advanced stages of their evolution resulting in late arrivals to the ED.[20]

Deficits not detected by the NIHSS or minor symptoms before the start of infusion were the second most frequent exclusion criteria. In 27% of SM patients, their symptoms mimic those of posterior territory circulation with vertigo, acute loss of balance, or dysarthria, which have absent or low representation in the NIHSS[21]—excluding them from thrombolytic therapy.

Finally, rapidly improving symptoms was the third most important exclusion criterion, probably equivalent to the improvement of the aura of a migraine attack or the resolution of Todd's paralysis after a seizure. When patients are evaluated after their symptoms have improved, they have no measurable NIHSS deficits, which excludes them from therapy. All other exclusion criteria were infrequent and do not represent >9% of cases.

Table 3. *Symptoms of patients with stroke mimics arriving to the emergency department*

Symptoms of stroke mimic arriving to the ED	n (%)
Aphasia	43 (37.6)
Symptoms mimicking posterior circulation	31 (27.5)
Paresis	17 (15.6)
Pure hypoesthesia	6 (5.5)
Other symptoms	16 (13.8)

Abbreviation: ED, emergency department.

Table 4. *Exclusion criteria for thrombolysis in stroke mimics*

Exclusion criteria	n
Outside of the thrombolytic window	96
Deficits immeasurable by NIHSS or minor before the start of infusion	37
Rapidly improving symptoms	7
Coagulation abnormalities	3
Seizure at the beginning of the episode	2
Recent ischemic stroke	2
Recent intracranial bleeding	1
Recent surgery	1
High blood pressure not able to be controlled with medication	1
Age >80 years (ECASS III criteria)	1
Known giant brain arteriovenous malformation	1

Abbreviations: ECASS, European Cooperative Acute Stroke Study; NIHSS, National Institutes of Health Stroke Scale.

As seen in previous studies, patients with SM more frequently presented beyond the therapeutic window, had lower NIHSS scores, and had negative DWI studies in comparison with stroke patients, a finding that has already been described by others.[1-9] In our patients, SM cases were less prone to arrive in the first 270 minutes of the beginning of their symptoms or had a NIHSS stroke scale score >10. In addition, they suffered less frequently from hypertension[22] and were more often diabetic. Seizures (19.3%) and migraine (10.1%) were also frequent causes of SM, similar to what has been described by others,[1-9] with aphasic symptoms being the predominant clinical presentation as described by other authors.[5,9]

Based on the current information, a neurologist faced with a patient with an acute focal deficit suspicious of acute ischemic stroke that fulfills the criteria for thrombolysis should not hesitate to use this treatment because the patient probably does have a stroke; SMs have many contraindications that exclude them from rt-PA, and if the patient is ultimately diagnosed as a SM—as shown by Chernyshev et al,[7] Tsivgoulis et al,[8] and Guillan et al[9]—intravenous thrombolysis appears to be safe in these patients, without the risk of cerebral hemorrhagic complications and favorable prognosis. Delaying or withholding treatment because the patient could be diagnosed as a SM is inappropriate and does not follow the principle of "time is brain."

The main strengths of our study are the large sample size in a center where rt-PA is performed routinely and patients are studied with a neuroimaging protocol that allows the rapid detection of haemorrhages, ischemia, and vessel occlusions.

Our study also has some limitations; it is a single-center study in which all patients with neurologic symptoms remotely suggesting a stroke are seen by a stroke neurologist with stroke fellows on call. Therefore, our experience may not be representative of the realities of many hospitals. We also cannot exclude that in some cases seen as isolated vertigo or functional disturbances, DWI and vascular imaging were used to avoid categorizing these patients as SMs. However, this seems unlikely because 10% of our SM patients had normal DWI and vascular imaging at the time of arrival to the ED >24 hours after the first symptoms and nevertheless were considered initially to be stroke cases. This points to the fact that neurologists used clinical approaches to reach the diagnosis of stroke. In our stroke prospective database, symptoms were not recorded and therefore we cannot compare their symptoms with those of the SM patients. In addition, we do not usually record the numbers of eligible stroke patients who refuse rt-PA therapy.

In conclusion, patients with a diagnosis of SM frequently had exclusion criteria for systemic thrombolysis, including presenting beyond the current thrombolytic window, having immeasurable symptoms according to the NIHSS, and rapidly resolving focal neurologic symptoms.

References

1. Hemmen TM, Meyer BC, McClean TL, et al. Identification of nonischemic stroke mimics among 411 code strokes at the University of California, San Diego, Stroke Center. J Stroke Cerebrovasc Dis 2008;17:23-25.
2. Hand PJ, Kwan J, Lindley RI, et al. Distinguishing between stroke and mimic at the bedside: The Brain Attack Study. Stroke 2006;37:769-775.
3. Libman RB, Wirkowski E, Alvir J, et al. Conditions that mimic stroke in the emergency department. Arch Neurol 1995;52:1119-1122.
4. Ay H, Buonanno FS, Rordorf G, et al. Normal diffusion-weighted MRI during stroke-like deficits. Neurology 1999;52:1784-1792.
5. Winkler DT, Fluri F, Fuhr P, et al. Thrombolysis in stroke mimics: Frequency, clinical characteristics, and outcome. Stroke 2009;40:1522-1525.
6. Uchino K, Massaro L, Hammer MD. Transient ischemic attack after tissue plasminogen activator: Aborted stroke or unnecessary stroke therapy? Cerebrovasc Dis 2010;29:57-61.
7. Chernyshev OY, Martin-Schild S, Albright KC, et al. Safety of tPA in stroke mimics and neuroimaging-negative cerebral ischemia. Neurology 2010;74:1340-1345.
8. Tsivgoulis G, Alexandrov AV, Chang J, et al. Safety and outcomes of intravenous thrombolysis in stroke mimics: A 6-year, single-care center study and a pooled analysis of reported series. Stroke 2011;42:1771-1774.
9. Guillan M, Alonso-Canovas A, Gonzalez-Valcarcel J, et al. Stroke mimics treated with thrombolysis: Further evidence on safety and distinctive clinical features. Cerebrovasc Dis 2012;34:115-120.
10. Lövblad KO, Laubach HJ, Baird AE, et al. Clinical experience with diffusion-weighted MR in patients with acute stroke. AJNR Am J Neuroradiol 1998;19:1061-1066.
11. Toi H, Uno M, Harada M, et al. Diagnosis of acute brainstem infarcts using diffusion-weighed MRI. Neuroradiology 2003;45:352-356.
12. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen

activator for acute ischemic stroke. N Engl J Med 1995; 333:1581-1587.
13. Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med 2008;359:1317-1329.
14. Grimm SA, DeAngelis LM. Intratumoral hemorrhage after thrombolysis in a patient with glioblastoma multiforme. Neurology 2007;69:936.
15. Brunser AM, Lavados PM, Cárcamo DA, et al. Additional information given to a multimodal imaging stroke protocol by transcranial Doppler ultrasound in the emergency room: a prospective observational study. Cerebrovasc Dis 2010;30:260-266.
16. Alexandrov AV, Molina CA, Grotta JC, et al. Ultrasound-enhanced systemic thrombolysis for acute ischemic stroke. N Engl J Med 2004;351:2170-2178.
17. Riggs JE. Neurologic manifestations of electrolyte disturbances. Neurol Clin 2002;20:227-239.
18. Krause GS, White BC, Aust SD, et al. Brain cell death following ischemia and reperfusion: A proposed biochemical sequence. Crit Care Med 1988;16:714-726.
19. Häussinger D, Schliess F. Pathogenetic mechanisms of hepatic encephalopathy. Gut 2008;57:1156-1165.
20. Durand ML, Calderwood SB, Weber DJ, et al. Acute bacterial meningitis in adults. A review of 493 episodes. New Engl J Med 1993;328:21-28.
21. Sato S, Toyoda K, Uehara T, et al. Baseline NIH Stroke Scale Score predicting outcome in anterior and posterior circulation strokes. Neurology 2008;10:2371-2377.
22. Sacco RL, Benjamin EJ, Broderick JP, et al. IV. Prevention and rehabilitation of stroke. Risk factors. Stroke 1997; 28:1507-1517.