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

Alejandro M. Brunser, MD,* Sergio Illanes, MD,* Pablo M. Lavados, MD, MPH,* Paula Muñoz, MD,* Daniel Cárcamo, MD,* Arnold Hoppe, MD,* Verónica V. Olavarria, MD,* Iris Delgado, MSc,† and Violeta Díaz, MD*

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

From the *Cerebrovascular Program, Neurology Service, Department of Internal Medicine, Clínica Alemana de Santiago; and †Epidemiology and Public Health Policy Center, Facultad de Medicina, Department of Academic and Scientific Development, Clínica Alemana, Universidad del Desarrollo, Santiago, Chile.

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Address correspondence to Alejandro M. Brunser, MD, Director Neurosonology Laboratory, Cerebrovascular Program, Neurology Service, Department of Internal Medicine, Clínica Alemana de Santiago, Facultad de Medicina Clínica Alemana, Universidad del Desarrollo Santiago Chile, Av Manquehue Norte 1410, 10th floor, Vitacura 7630000, Santiago, Chile. E-mail: abrunser@alemana.cl.

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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%).